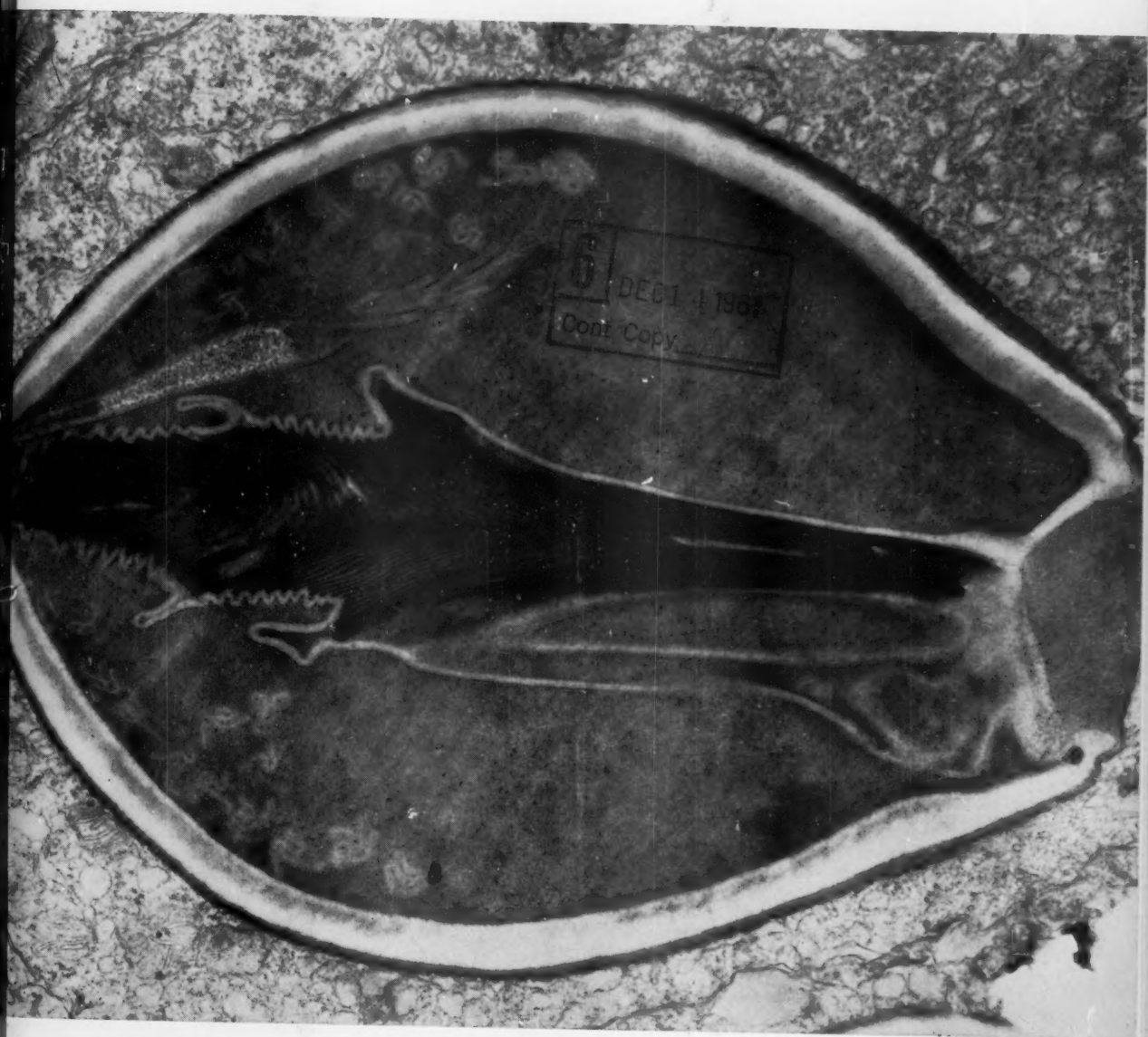
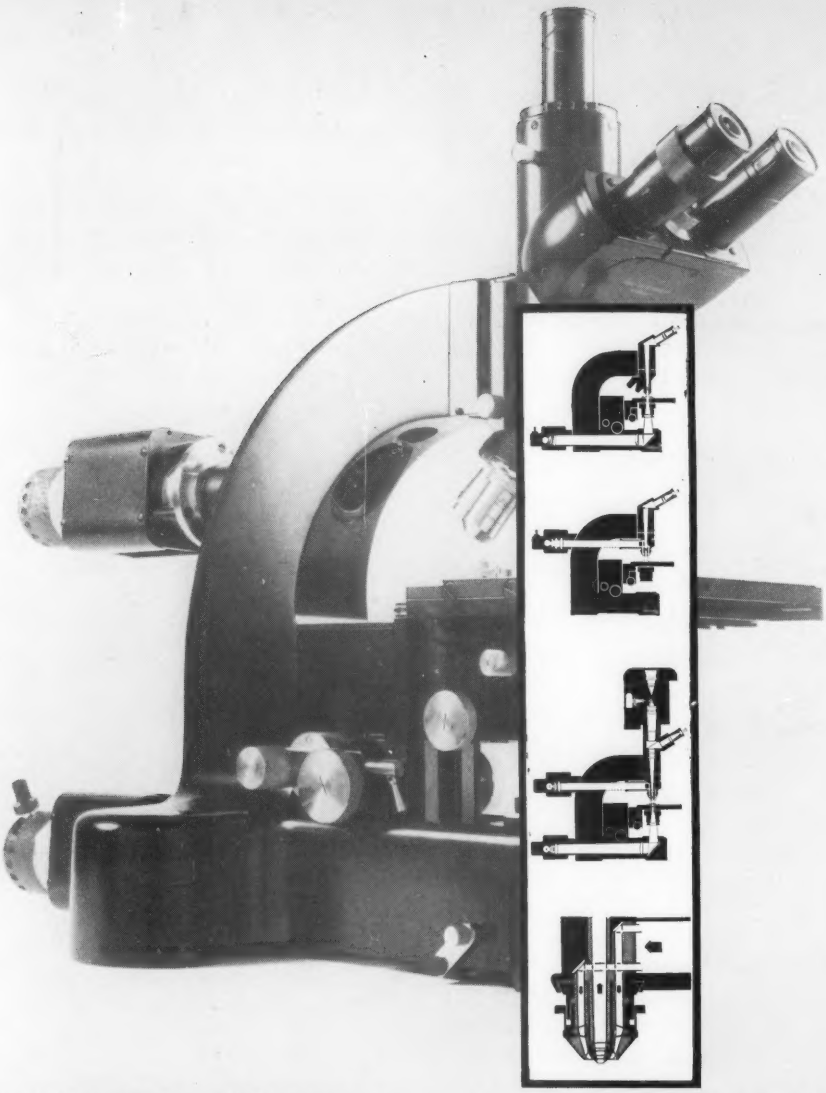
SCIENCE

15 December 1961

Vol. 134, No. 3494

AMERICAN ASSOCIATION FOR THE ADVANCEMENT OF SCIENCE





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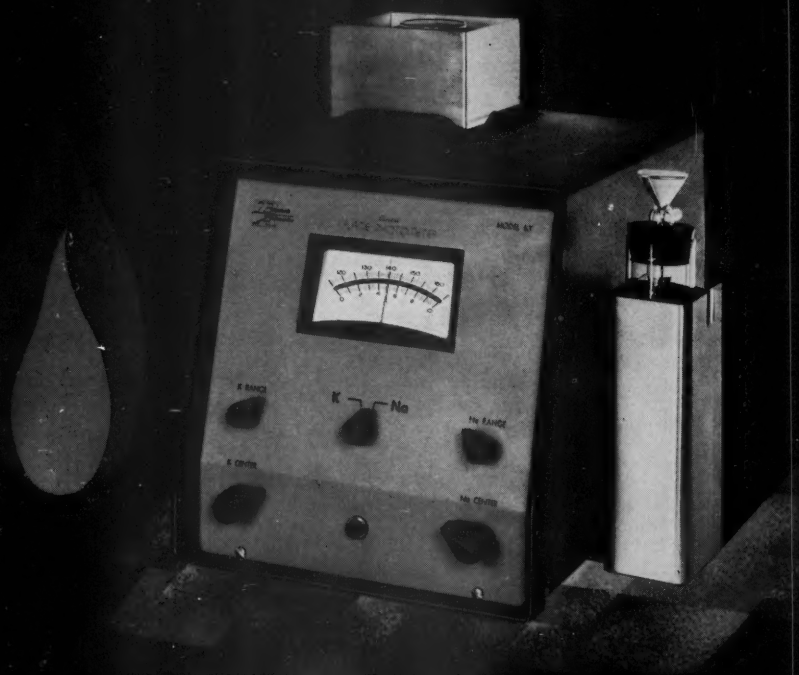

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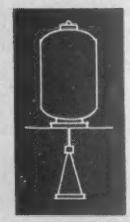

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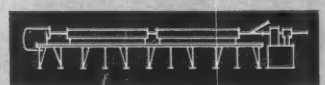

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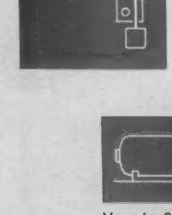

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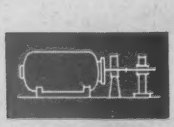

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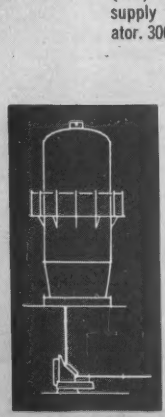

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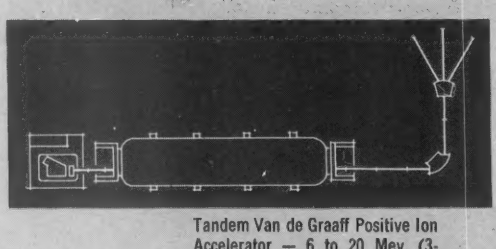

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Better Nothing Than Something?

One argument that has been directed against present civil defense efforts is that the program, by giving us a false sense of security, will increase the likelihood of atomic war. Admittedly, the various statements and actions by various people in the government are at such odds that we are forced to wonder just what our civil defense program really is. But if we understand the basic objectives of the program to be those set forth by President Kennedy in his special message last May—a fair assumption—then this particular argument against civil defense is not convincing.

In the message, the President draws a distinction between deterrence and insurance. Our deterrent policy depends on a potential enemy responding rationally to the fact that, if his attack means our utter devastation, it also means his utter devastation at the hands of our retaliatory forces. But suppose another country acts irrationally, miscalculates, or launches an attack by accident? The civil defense program is conceived as insurance against this contingency. A shelter program, for example, could protect a part of the population against fallout, should the attack be of the kind that produces this hazard.

The argument that the present civil defense program will increase the likelihood of war seems to hinge on the supposition that the scope of the program will be misunderstood in a special way. The misunderstanding will be to attribute greater security to the program than it provides. This false sense of security will then lead us to indulge in a greater degree of brinkmanship than we would otherwise risk. With all the comfortable hustle and bustle that goes with carrying out civil defense, people will forget that the protection offered is only for a limited portion of the population, for the barest sort of survival, and against only certain kinds of attack.

There is plenty of evidence that the implications of the civil defense program have not been fully understood by the man in the street or, for that matter, by the New Frontiersmen responsible for getting the program going. In support of the latter contention, consider the delay in producing the famous booklet that was promised to explain everything. The delay can only mean that the policies for carrying out the basic objectives have not been worked out. The problem of preparing the booklet cannot simply be one of translating government jargon into English.

But because we are not doing well in the program, it does not follow that we cannot do better. Is the distinction beween insurance and deterrence really so hard to grasp? It would seem to be comprehensible to any reader of one of the popular news weeklies. The basic ideas are not so foreign to us. When we take out accident insurance we do not regard our policy as a deterrent to motorists who might otherwise run us down. Why, then, if we are told that atomic war could mean the destruction of our civilization, should we forget that fact as soon as we are also told that a modest number of people who might otherwise perish could possibly be saved if we take proper precautions now?

It may be that civil defense will give us a false sense of security, but an equally good hunch is that once the program is fully under way its psychological impact will be somewhat different. It may make many people look squarely for the first time at the consequences of atomic war.
—J.T.

15 December 1961, Volume 134, Number 3494 SCIENCE

The Competitive World of the Pure Scientist

The quest for prestige can cause conflict between the goals of science and the goals of the scientist.

F. Reif

The "pure scientist" is likely to be pictured as a person who devotes himself to the study of natural phenomena without regard to their possible practical or technological applications. Motivated by intellectual curiosity and immersed in his abstract work, he tends to be oblivious of the more mundane concerns of ordinary men. Although a few older scientists have become active in public affairs in recent years, the large majority who remain at work in their university laboratories lead peaceful lives, aloof from the competitive business practices or political manipulations of the outside world.

Stereotype versus Reality

There is some truth in this stereotyped portrait. But if a young student took its apparent serenity too seriously, he would be forced to revise his perspective very early in his scientific career. The work situation of the scientist is not just a quiet haven for scholarly activity, ideally suited to those of introverted temperament. The pure scientist, like the businessman or lawyer, works in a social setting, and like them, he is subject to appreciable social and competitive pressures. The institutional framework within which he functions is distinctive; it is basically the university system. Furthermore, his competition does not resolve primarily around money; there is no very direct relationship between the quality of the scientist's professional performance and the economic rewards he receives. But competition need not be confined to the acquisition of wealth or political power. It is, therefore, of particular interest to discover how intense competition can become in an area as remote as pure science. In recent years rapid expansion has occurred in many branches of science. More scientists are active in many fields, more laboratories (including some in industry and government) engage in pure research activities, and more dollars are spent on such research. While this expansion has given the scientist a more prominent social role, it has also intensified the competitive pressures under which he works.

A few examples will illustrate how such competition can manifest itself. I shall take these illustrations from the field of physics, because physics is a well-developed pure science and because this is the field with which I am most familiar. In this country research work in physics has traditionally been published in a bimonthly journal called the *Physical Review*. In addition to full-length research reports, this journal used to publish "Letters to the editor," short notes whereby scientists could briefly communicate important new developments. The time elapsed between submission of a manuscript and its appearance in print was approximately 5 months for a regular paper and 2 or 3 months for a "letter." But in a period of rapid growth and development the pressure to publish fast and to establish priority claims became sufficiently great to make the *Physical Review* appear an inordinately slow medium of communication. Three years ago, therefore, its editors decided to eliminate the "Letters" section and to found a separate bimonthly journal, the *Physical Review Letters*, devoted entirely to the fastest possible publication of short notes on important discoveries. The time between submission of a manuscript and its appearance in print has been reduced to as little as 4 weeks! Not only is the existence of such a journal a significant phenomenon in itself; it has also necessitated the formulation of new editorial policies. As a result, although editorials in scientific periodicals are ordinarily very rare, some illuminating examples have found their way into issues of the *Physical Review Letters*.

In one of these (*1*) the editor comments that a large number of manuscripts are submitted whose importance and meagre content are not adequate to justify publication in the *Letters*. He goes on to say: "When a 'hot' subject breaks there is a deluge of follow-up contributions. . . . With the rapid exploitation of new ideas, priority questions become serious problems. Possibly important technical applications often lurk in the background. . . ." After explaining that he feels compelled to reject as unworthy of publication more than 40 percent of the manuscripts received, he concludes: "We do not take kindly to attempts to pressure us into accepting letters by misrepresentation, gamesmanship, and jungle tactics, which we have experienced to some (fortunately small) extent."

From the foregoing comments it is apparent that scientists seem most eager to see their work appear in print as soon as practicable. But to achieve that purpose, even the *Letters* can appear unduly slow. Certainly, the daily press is even faster; and though it may be less

The author is associate professor of physics, University of California, Berkeley.

suitable for erudite publication, it is more effective for publicity and no less effective for establishing priority. Consequently, there have been several instances in recent years when important discoveries in physics were first announced in the New York *Times*. This procedure is not, by traditional values of the scientific community, considered to be very ethical. Nor is it, as the *Letters* editor points out in another editorial, an activity to be confused with the well-developed public information and publicity activities carried out by his own office and by such agencies as the American Institute of Physics. The editor expresses himself quite forcefully (*2*): "As a matter of courtesy to fellow physicists, it is customary for authors to see to it that releases to the public do not occur before the article appears in the scientific journal. Scientific discoveries are not the proper subject for newspaper scoops, and all media of mass communication should have equal opportunity for simultaneous access to the information. In the future, we may reject papers whose main content has been published previously in the daily press."

In the passages quoted, the editor of the official journal of American physicists makes some revealing comments about the behavior of his fellow scientists. What are some of the factors responsible for such behavior? Why should there be this exorbitant desire to publish and to do so ahead of others? The following discussion will focus attention on some of these questions in an attempt to clarify the conditions of modern science which contribute to this behavior. We shall first examine the great importance of prestige to the scientist. It will become apparent that the scientist carries out his work in a setting where he is extraordinarily dependent on the good opinion of others, and where his reputation becomes translated into many concrete consequences for him. Personal recognition thus assumes even more importance for the scientist than for most other people, and he competes persistently to achieve maximum prestige. I shall illustrate how this competition takes place and how it affects the manner in which scientific research is carried on. Finally, we shall ask how the existence of such competition serves to advance or impede scientific activity. This question will reveal the existence of some conflicts between these competitive pressures and scientific work proper. Throughout this discussion it should be borne in mind that the situation is not static and that the rapid expansion of science has made many of these problems more conspicuous than they were a few years ago.

Prestige and Success

The scientist is not different from others in his desire to be successful, but his definition of "success" has some distinctive features. The work of the pure scientist is abstract; it consists essentially only in gathering new data and formulating new concepts. To constitute scientific knowledge, these must be verifiable by other scientists and usable by them as the basis for further exploration. Thus, the very nature of scientific activity implies the need for recognition of the value of one's work by others in the field. Furthermore, success in such activities is not readily measurable in quantitative terms recognized by all. It does not revolve around tangible things such as amount of money earned or number of factories owned. Only other scientists in his field can understand the scientist's work and judge its merits. Indeed, throughout his life the scientist is dependent on the good opinion of significant other scientists for practically everything he does or hopes to attain. A review of the scientist's professional career will illustrate the truth of this statement.

While still in high school, the scientist-to-be becomes aware that competition and prestige will affect his future success. He must strive for good grades in order to be admitted to college and later to graduate school. He realizes the importance of attending a college of high reputation, not only because it will provide him with a better education but also because it will facilitate his later admission to a good graduate school. Finally, he must earn the good opinion of his teachers to secure the letters of recommendation which will help him enter college and gain scholarship grants or prizes.

After the student obtains his Ph.D. degree, his dependence on the good opinion of others is by no means ended. His first task is to find a suitable position. Characteristically, jobs in the better universities or in top industrial research laboratories are practically never advertised but are handled by personal communication between well-established scientists, who inquire informally whether their colleagues happen to know of some candidates for a given position or have an opening in their organization for a particular candidate. The job-seeking scientist is clearly in a more advantageous situation if he comes from a well-known institution and has been associated with a scientist of reputation. Invariably it is essential to him that there should be prominent scientists in the world who are willing to comment favorably upon the quality of his work. In most cases, before an appointment is decided upon, the hiring institution formally requests letters of recommendation concerning the candidate from several such prominent scientists. It is thus very important for the scientist to create, either through personal contact or through published work, a favorable impression among as many key scientists as possible.

Professional mobility of the scientist depends, therefore, in an essential way on the reputation he has acquired among prominent people in his field. This is true when he is securing his first job and true in his subsequent moves from one position to another. (In this connection it may be remarked that to move from an institution of high prestige to one of lower prestige is significantly easier than to move in the reverse direction.) Promotion to higher academic rank is subject to similar criteria. Again the university requests letters of recommendation from outside scientists and in some cases may appoint reviewing committees before deciding to promote someone to a tenure position. Even when the scientist has obtained a full professorship he has not reached the end of possible advancement based on his reputation. Within the academic hierarchy there are still some "name" professorships, or ultimately some administrative posts such as dean or university president. In these days of increasing importance of science in world affairs there are also potential opportunities in government—for example, advisory positions to the President or appointments to some such agency as the Atomic Energy Commission. Industrial organizations, as well, may offer key positions, such as the directorship of a research laboratory. Needless to say, the academic promotions which the scientist achieves carry with them increased financial rewards and, at the higher ranks, the security of a permanent position.

To carry on his work, the scientist needs money and adequate research

facilities. Since World War II the financial expenditures required to perform the increasingly complex research of modern science have become so great that universities can provide only a very small fraction of the necessary funds. The remainder must come from outside sources—some of them private foundations but by far the greatest number government agencies such as the National Science Foundation, the Atomic Energy Commission, or the Office of Naval Research. On what basis do all these groups award their available funds to individual investigators? The usual procedure is to send the research proposal of the investigator to some prominent scientists for review. These scientists then make appropriate recommendations based on their evaluation of the specific proposal and their opinion of the merits of the scientist submitting it. The scientist today is thus increasingly dependent upon the reputation he has established among his colleagues to obtain the very means necessary for carrying out his work: funds for buying equipment and supplies and for paying the salaries of the personnel in his research group. In addition, the scientist's prestige helps him attract good and numerous students and postdoctoral fellows who can be of significant assistance in furthering his research program.

At times the scientist may be interested in obtaining a fellowship or grant —for example, a Guggenheim or National Science Foundation senior postdoctoral fellowship. Grants of this nature permit him to travel abroad for a year; or spend some time at a different university, where he can learn new techniques; or gain temporary relief from teaching duties to devote himself full time to his research. In applying for such a fellowship, the scientist will again be judged by some select prominent scientists, and once more his reputation among these scientists determines whether the award will be made to him.

The prestige acquired by the scientist very directly influences the likelihood of his nomination by fellow scientists for special honors or distinctions. Examples are the award of a Nobel prize or selection to membership in the National Academy of Sciences. Selection to serve as an officer of the national scientific organization is another recognition of distinction. The scientist's prestige may also lead to special invitations to attend scientific conferences as guest speaker or to join another university as visiting professor; finally, it may result in offers of remunerative consultantships in industry.

I think it is worth while, before leaving this discussion of the prestige system, to remark on a few of its peculiarities. One of these is the "positive feedback" involved—the fact that the possession of prestige tends to facilitate the acquisition of further prestige. For example, a person of prestige is likely to be affiliated with one of the better-known institutions, likely to obtain more funds to do effective research, and likely to attract better students—all of which circumstances, of course, tend to enhance his prestige even further. There is a similar relation between the prestige of individuals and the prestige of institutions. Institutions of good reputation can attract individuals of distinction whose presence, in turn, lends increased prestige to the institution.

Another feature of interest concerns the people who set the standards against which the individual scientist appraises himself and whose opinion determines his general reputation in the field. It is mainly the well-established scientists in the major universities of the world who set these standards. Since the institution with which the individual scientist is affiliated tends to evaluate him chiefly on the basis of his reputation, it becomes of greater concern to the individual to seek the good opinion of people on the national or international scene than to strive for accomplishments which attract only local attention. The scientist thus tends to have stronger loyalty to his field than to the specific institution of which he is a member. This is particularly true in the present days of expansion, when there is great mobility between different positions. The trend, in the major universities of this country, to minimize the importance attached to the teaching functions of the faculty reflects the situation. Teaching undergraduates is a local activity which may be appreciated by the students but does not serve to enhance the scientist's international prestige, on the basis of which the university will decide whether he is worthy of promotion. "Research and the training of graduate students are valued highly by the faculty; teaching, by contrast, is second-class. . . . It is a more usual, and probably a more realistic, view that time taken for teaching is time stolen from research, and that the road to academic heaven is paved with publications" (*3*).

The growing importance of science has also led to a proliferation of industrial research laboratories. The oldest and most distinguished of these are active in pure research and are staffed by some very competent persons who might readily have joined a university had opportunities in industry not been available. These people are eager not to be considered inferior by the rest of the scientific community, despite their industrial affiliation. Hence, they adopt for themselves standards very similar to those prevalent in the universities and compete within the same prestige system. This also preserves their mobility and leaves open the road back into some university position. Since the pure scientist's reputation, irrespective of the particular institution to which he belongs, is determined by the same reference group of prominent scientists, there exists a common prestige system which cuts across purely organizational lines. Thus, more prestige may be attached to a good position at a major university than to one in an industrial laboratory, but a position in a top industrial or government laboratory carries more prestige than one in a smaller university.

Publishing "Fustest and Mostest"

Because the social context within which the scientist receives his training and does his research is one where the possession of prestige is highly rewarded, competition among scientists is largely directed toward the acquisition of prestige. The particular forms assumed by this competition are determined by the nature of the scientific discipline and the character of the institution where the scientist carries out his work. A scientist strives to do research which he considers important. But intrinsic satisfaction and interest are not his only reasons. This becomes apparent when one observes what happens if the scientist discovers that someone else has just published a conclusion which he was about to reach as a result of his own research. Almost invariably he feels upset by this occurrence, although the intrinsic interest of his work has certainly not been affected. The scientist wants his work to be not only interesting to himself but also important to others. He wants it to attract the maximum attention from other

people, and in this quest priority is a crucial factor. An important discovery becomes intimately associated with the name of the scientist responsible for it. If somebody else makes this same discovery at about the same time, several names become attached to it and the contribution to his own prestige is correspondingly diluted. The chances of receiving a Nobel prize or a promotion are similarly decreased. Finally, if someone else succeeds in making this discovery a few months or weeks before he does, almost all of the scientist's efforts on the problem have come to naught. He may not even be able to publish his own results, since they may then represent only uninteresting duplication of work already in the scientific literature. Under the circumstances, it is not surprising if the scientist sometimes works at feverish speed under constant fear that he may be "scooped." Even a couple of weeks' delay can sometimes make a difference!

Being the first to make an important scientific contribution is, of course, only one way of obtaining recognition. For a scientist to be on the verge of making some discovery of far-reaching implications is relatively rare. Most of the time he is engaged in the less spectacular task of doing useful work leading gradually to increased knowledge. In this situation the most effective way to attract the continuing attention of other scientists is to publish as many papers as possible, to attend numerous scientific meetings, and to give many talks on one's research. The great emphasis on publishing copiously is exemplified by a motto familiar to all young faculty members—"publish or perish"— a phrase that well illustrates how the young scientist feels about the competitive pressures to which he is subject. Under the "up-or-out" rule, common in large universities, instructors and assistant professors are allowed only a fixed maximum number of years within their academic rank. If they are not promoted before the end of this time, their dismissal from the university is automatic. Whether or not an individual is promoted depends, of course, on the reputation he has achieved as a result of his publications.

Some of these competitive pressures have been familiar features of academic life for a long time. The expansion of scientific activity since World War II, has, however, significantly changed the conditions under which the scientist does his work. One consequence has been the emergence of new and intensified patterns of competition as the number of scientists at work in many areas has multiplied. Not only are more universities engaged in active research; more industry and government laboratories are also carrying out pure research of a type nearly indistinguishable from its academic counterpart. Many people in different institutions are thus likely to be working along fairly similar lines. Furthermore, the time lag between advances in basic science and the associated technological developments has become increasingly small. Sometimes new ideas or techniques arising in the work of the pure scientist may be such as to warrant patenting without further exploration. Even when potential technological applications are not immediately apparent, there are well-equipped industrial laboratories constantly poised to exploit all possible consequences of a basic advance. In addition, research has become an activity which involves the expenditure of large sums of money and which has come to attract attention even from the general public. Under these circumstances it is easy to understand why the scientist finds increasing difficulty in carrying out his work immune from outside pressures.

Rapid publication of results and questions of priority assume, therefore, great importance; nor is the need for a journal such as *Physical Review Letters* too surprising. No longer does a scientist study a topic at some length before publishing his findings in a paper or monograph. Instead, he tries to publish a note on a subject as soon as he obtains any result worth mentioning—and occasionally even before. The threat of someone else's getting there first is too great. At times a scientist may publish just a proposal for an experiment, merely pointing out that such an experiment might be interesting and feasible. To obtain preliminary experimental results before publishing anything may take too much time—time during which the scientist might "get scooped" by someone else. For similar reasons scientists may be led to engage in various practices which the editor of *Physical Review Letters* finds reason to discuss. In his words (*4*), there is the "author who uses the *Letters* merely to announce a later paper and whose Letter is incomprehensible by itself"; the "author who submits many Letters hoping that statistics rather than quality will cause one to be accepted"; or the "author who tries to sneak a Letter in to 'scoop' a competitor who has already submitted an Article."

The emergence of rapidly changing "fashionable areas" of scientific activity is still another consequence of the expansion of science. In a highly developed discipline such as physics, genuinely new ideas or unexpected breakthroughs are not really very common. When such a discovery does occur, many people are eager to drop more routine work in order to explore the potentially important consequences of the new development. Present conditions are also such as to permit a substantial number of scientists to shift their field of research quite rapidly. One reason is that the major university and industrial laboratories provide the flexibility of a large variety of experimental facilities and adequate manpower resources. Moreover, since work is often proceeding along similar lines in a number of different laboratories, scientists active in areas related to the discovery are in a particularly good position to turn their attention to an investigation of its consequences. Every new discovery, therefore, results in a burst of intense and very competitive activity. In physics there ensues a profusion of "Letters," until the editor decides that the subject has become sufficiently old to be routine. Since so many people concentrate their efforts in one area, the road from the novel to the routine is often traveled in a few months.

The preceding discussion illustrates the increasingly important role played in modern science by large-scale research organizations. This is true not only in industrial and government laboratories but also in the universities, where specialized research institutes have become quite common. Here the scientist is usually a member of some group organized around a particular project or a special research facility, such as a high-energy accelerator, and work is often done jointly by several people. An experiment was recently reported in a "Letter" by no less than 24 coauthors! Working under these conditions is appreciably different from the individualistic endeavors prevalent 10 or 20 years ago, and the scientist must compete in some novel ways. He must establish an individual reputation even though he works as a member of a larger group. He also has to compete in a setting which tends to be organized along hierarchical lines, where scientists in the top positions determine policy

and the direction of research. Finally, many members of research institutes constitute a "secondary faculty" of research associates. They do not teach or belong to a department, nor do they have permanent positions. If they hope to gain the security of a tenure position they must strive for sufficient eminence to be appointed to regular academic rank.

Conflicting Values

After this description of the existing conditions in pure science, let us consider some of the consequences of competition in this area. This competition certainly affects the functioning of scientific research in several beneficial ways. The prestige system helps to maintain high standards of accomplishment which reflect the collective judgment of important scientists and are therefore fairly uniform throughout the world. Prestige accrues predominantly to those whose discoveries prove fruitful as a basis for further work by other scientists. Specific areas of activity in science thus become fashionable not just because they are novel and different but because they are likely to lead to scientific contributions of permanent value. Even when current fashion leads to duplication of work by different investigators, the resulting critical checking of results may occasionally help in avoiding mistakes and oversights. Competition under these conditions encourages continuing active exploration as well as rapid and thorough exploitation of all new discoveries. Research institutions have become well adapted to carry out these functions. Not only are they well equipped and staffed but they are capable of using their resources with considerable flexibility.

On the other hand, the competitive atmosphere has results which are less desirable. It subjects the individual scientist to appreciable strains, thus increasing further the demands made upon him by an already rigorous scientific discipline. But apart from such psychological effects, there are possible deleterious consequences affecting his research activity itself. These are usually the result of conflicts between the requirements of the scientific work proper and the pressures of competition. To the individual scientists they may appear as conflicts between the values inherent in science and more selfish personal values.

One such conflict is that of reflection versus production. The scientist may desire to take some time to think and speculate; he may want to get a fresh point of view by reading about developments outside his special field and to discover suggestive analogies worth pursuing; or he may be tempted to undertake an experiment sufficiently novel in character for him to be uncertain about its ultimate feasibility. Activities of this kind are potentially fruitful precisely because they focus attention upon lines of investigation off the beaten track. But, by the same token, they are also risky, since in many cases they may lead to no results at all. In order to make his reputation with a steady stream of publications, it is safer for the scientist to work along more conventional and familiar lines, where he has greater assurance of obtaining results. Young scientists are in a particularly vulnerable situation. Since they must establish their reputation in a relatively short period of time to achieve a permanent academic position, undertaking risky projects during this period is dangerous. Interesting in this connection are instances where a fundamental discovery is made by someone in a small laboratory in an out-of-the-way place. As soon as the result is published, many big laboratories employ their superior facilities to exploit the consequences of the discovery so effectively that the scientist originally responsible for it finds it difficult to compete with them. People in the big laboratories had available, of course, all the resources necessary to make the original discovery themselves, but they used them less imaginatively. Organizations well adapted to the exploitation of a field in which the direction of approach has become clear are not necessarily the best for stimulating exploration of the genuinely unknown.

A further conflict, which may lead to slipshod work when competitive pressures are pronounced, is that of careful versus fast work. Another *Letters* editorial describes the dilemma succinctly (*5*). "One of our most ticklish problems concerns the large number of contributions that pour into our office when a 'hot' subject breaks and many groups initiate related work. . . Because of the rapid development, and the intense competition, we have found it necessary to relax our standards and accept some papers that present new ideas without full analysis, relatively crude experiments that indicate how one can obtain valuable results by more careful and complete work, etc.—in short, papers which under less hot conditions would be returned to authors with the recommendation that further work be done before publication. . . . Such incomplete papers have been accepted reluctantly since we realize that thereby we penalize some physicists who, working along the same lines, want to do a more complete job before publishing."

Another conflict is that of communication versus secrecy. It is intrinsic in scientific activity that knowledge and ideas are common property, to be shared and used by all scientists. But if scientist *A* has an interesting idea and describes it to scientist *B*, the latter may exploit it before scientist *A* himself can do so. It may then be better for *A* not to disclose his ideas before they are published and before his claim to priority is safely established. Closely related to this conflict is that of cooperation versus rivalry. Should scientist *A* tell scientist *B* about some new technique he has developed if *B* may use it in his own work to compete more effectively against *A*? Lack of full communication can, of course, slow down scientific progress. A significant amount of energy is diverted from struggling with the subject matter of science to fighting other people in the field.

There exist other conflicts, such as that between research and teaching. But instead of elaborating further, I might better give a specific example illustrating how the pursuit of a purely scientific problem can give rise to the competitive pressures described. A few years ago Mössbauer, a young German physicist, discovered that the radiation emitted by certain atomic nuclei in solids is characterized by an exceedingly well defined frequency. This observation suggested to several people, in particular to two scientists, *X* and *Y* (*6*), that such nuclei might be used as extremely accurate clocks well suited for checking a consequence of Einstein's general theory of relativity. This theory predicts that the rates of two identical clocks should be minutely different if they are located at different heights in a gravitational field. Both *X* and *Y* undertook to check this prediction experimentally. Scientist *X*, however, first published a "Letter" outlining his proposal for the experiment, long before he was ready to obtain actual data. A few weeks later, again before either *X* or *Y* had published any preliminary results in the scientific literature, the

front page of the New York *Times* carried a picture of scientist *X*, together with an article describing the experiment he was undertaking. When *X* discussed his experiment at a scientific meeting 6 weeks later he reported reluctantly that, despite hard work at great speed, he had not yet been able to reach any conclusions. At the same meeting *Y* announced that he had successfully carried out the experiment and obtained results in agreement with the theory; shortly thereafter *Y* published his findings. It was not until some 2 months later that *X*, in a "Letter," was able to report his own experiment, which also confirmed the theoretical expectation. He pointed out, however, the necessity of controlling the temperature of the experiment quite carefully to avoid introducing large extraneous effects; indeed, since *Y* had not taken such precautions, his findings lacked significance. In this instance an important experiment was performed in a short time and ultimately in a reliable way. But the example shows vividly the actual circumstances under which the experiment was carried out—the announcement of an experiment before it was undertaken, the newspaper publicity, the hurried activity of two scientists working under pressure to be the first to publish—and the lack of sufficiently careful work which may result from these conditions.

While much more could be said about the differing patterns of competition in various sciences and about the rapid changes taking place in many of these disciplines, my aim has not been to treat the topic exhaustively. It is sufficient if the perspectives of the outside observer have been broadened, to make him aware that the scientist is not just somebody concerned with new ideas and techniques, but that he carries out his work in a human, and sometimes all too human, context.

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Chemical Factors Controlling Nerve Activity

Analysis reveals the underlying chemical system that generates the currents responsible for nerve impulses.

David Nachmansohn

One of the characteristic features of living cells is their high potassium ion (K^+) concentration in contrast to the low K^+ concentration in the outer environment. The reverse is true for the sodium ion (Na^+) concentration. However, only conducting cells, nerve fibers, and muscle fibers make use of these concentration gradients for generating the electric currents which propagate impulses. These currents are carried by ions. During activity, Na^+ moves into the interior, and this movement is followed by an outflow of an equivalent amount of K^+ (*1*). There is a strong and rapid rise of sodium conductance and an equally rapid return to the initial stage. Subsequently, potassium conductance, already high in the resting state, increases but slightly, and the changes are relatively slow (*2*). These facts raise immediately the fundamental question: What is the special mechanism which enables conducting cells to use ionic concentration gradients, the source of electromotive force, for the generation of electricity?

It is difficult to see how electricity in a fluid system such as the living cell can be generated without chemical reactions. Conducting cells must be endowed with a special chemical system controlling the movements of ions in a specific way. Any doubt as to the chemical nature of this process has been removed by the recent heat-production measurements of A. V. Hill and his associates (*3*). They found that the initial heat can be separated into two phases: a strong positive heat, coinciding with electrical activity, followed by a negative heat during recovery. The conducting membrane is only 50 to 100 angstroms thick. Per gram of active material, the positive heat amounts to about 3 millicalories. This is about the same amount of heat as that produced per gram of muscle during a twitch.

What is the chemical reaction? About 30 years ago, acetylcholine was linked to a special phase of nerve activity. It was assumed to be released from nerve endings and to act as a neurohumoral transmitter on the effector cell, nerve or muscle. The observations were based on classical methods of pharmacology. However, the idea of a special mechanism at nerve endings which is basically different from that in axons was opposed by many electrophysiologists. The facts were not questioned, but the interpretation was. A new approach appeared imperative.

The rapid development of biochemistry, especially the spectacular rise of protein and enzyme chemistry during the last few decades, has provided powerful tools for analyzing cellular function in terms of physics and chemistry. An approach with biochemical methods was initiated 25 years ago. The enzymes effecting hydrolysis and the formation of acetylcholine were analyzed, the sequence of energy transformations was established, and a number of chemical reactions were correlated with physical events. Central to these studies have always been the proteins and enzymes, especially those linked specifically to the action of acetylcholine. They have been isolated and purified from the

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electric organs of electric fish. This material is particularly suitable. The organs are the most powerful bioelectric generators created by nature and are, moreover, highly specialized in their function, but the electricity is nevertheless basically similar to that of nerve and muscle fibers. The organs contain only 2 percent protein and 93 percent water, and isolation of the proteins associated with acetylcholine action is thereby greatly facilitated. These organs have been used, since 1937, for the analysis of the chemical basis of bioelectricity. The information obtained from the analysis of the proteins in vitro has been applied wherever possible to the study of the events in the living cell.

It soon became apparent that the original theory must be modified. A new concept was proposed which explains the original observations and reconciles the facts with the views of electrophysiologists. The action of acetylcholine is an intracellular or, rather, intramembranous process. It is responsible for the sudden changes in conductance that take place in conducting membranes during activity. The acetylcholine system is the specific chemical system with which all conducting cells of the animal kingdom are endowed and which enables them to generate the electric currents which propagate nerve impulses (*4*, *5*).

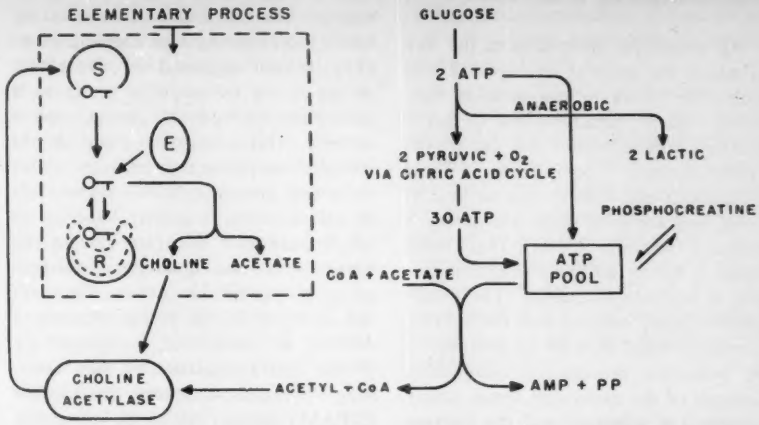


Fig. 1. Sequence of energy transformations associated with conduction and integration of the acetylcholine system into the metabolic pathways—a schematic presentation of the elementary process (see text). *S*, storage protein; *E*, cholinesterase; *R*, acetylcholine receptor protein, O⊤ acetylcholine. [Nachmansohn (*4*, *5*)]

The Acetylcholine System

The picture of the elementary process which has emerged from these studies may be described as follows (Fig. 1). Acetylcholine is bound, in resting condition, to some protein (or conjugated protein). Any stimulus reaching the membrane releases the ester, acetylcholine, which then reacts with a receptor protein. In this reaction some change of the protein is produced, probably a change of configuration. It is this reaction which is responsible for the increase in sodium conductance. It is the trigger by which the ionic concentration gradients, the potential source of electromotive force, become effective and by which the action currents are generated. The ester-receptor complex is in dynamic equilibrium with free ester and receptor protein; the free ester is attacked by cholinesterase (acetylcholine esterase) and rapidly inactivated by hydrolysis, the receptor—and the sodium conductance—being thus permitted to return to the original condition. The barrier is reestablished. The extraordinary speed of the hydrolysis by cholinesterase, which has a turnover time of 30 to 50 microseconds (*6*), permits the rapid restoration of sodium conductance. It explains the ability of nerve fibers to conduct several hundred or thousand impulses per second.

The development was reviewed, in 1959, in a monograph (*5*). In the present article some recent advances and new evidence for the concept proposed are discussed.

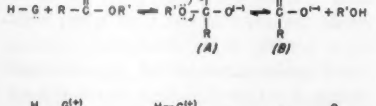
One of the major lines of evidence for the crucial role of the acetylcholine system in the generation of bioelectricity has been the demonstration that it is impossible under any condition to separate cholinesterase activity from electrical activity. If the picture of the elementary process proposed is correct, block of enzyme activity should stop electrical activity. A variety of extremely potent and specific inhibitors of cholinesterase have been applied to a great variety of fibers. In all types of fibers of the animal kingdom tested—central and peripheral, cholinergic and adrenergic, motor and sensory, vertebrate and invertebrate—electrical activity invariably failed when enzyme activity was blocked.

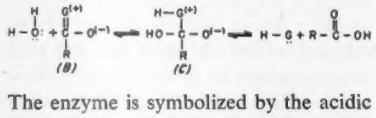
Some physiologists objected to this evidence on the basis that the concentrations of inhibitor used were unconventionally high, many times as high as at the nerve endings. It is not difficult to explain this apparent discrepancy. The conducting membrane of the axon, in contrast to that of the junction, is surrounded by structural barriers. The outside concentration is, therefore, irrelevant. Only the concentration at the site of action is pertinent. When the nerve axons are exposed, for instance, to 1 milligram of a powerful inhibitor of cholinesterase (such as diisopropyl phosphofluoridate) per milliliter, less than 1 microgram per gram is found inside the axon at the time when electrical activity fails. Moreover, a functional interdependence of electrical and chemical activity has been demonstrated in intact fibers. If electrical and chemical activity are measured in intact crab fibers exposed to inhibitors of cholinesterase, electrical activity fails when the enzyme activity falls to 20 percent of the initial level, regardless of the type of the inhibitor used and its concentration (*7*). Only the rate at which this level is reached varies.

Recently, a new and refined technique was used by Dettbarn (*8*). Electron microscope studies of Robertson (*9*) have shown that at the Ranvier nodes of myelinated frog nerve fibers the conducting membrane is covered by a thin and porous structure only. Using a single fiber of a frog sciatic nerve and applying Staempfli's technique to measure the electrical activity of a single Ranvier node, Dettbarn obtained, with 300 micrograms of eserine per milliliter, reversible block of electrical activity in 30 seconds. With 30 to 40 micrograms per milliliter, electrical activity is blocked in a few minutes. This effect is comparable to the conventional concentrations used on junctions. With the refined technique, a thousandfold increase in the potency of the inhibitor has been obtained.

Organophosphorus Compounds

An instructive illustration of the way in which the analysis of chemical and molecular forces in the proteins contributed to an understanding of nerve function resulted from the use of organophosphorus compounds. These compounds are widely used as insecticides, and some of them are potential chemical warfare agents. Their fatal action is due to the irreversible inactivation of acetylcholinesterase. The mechanism of their reaction with the enzyme became obvious once the mechanism of the hydrolytic process was established. Analysis of the molecular forces acting between the substrate and the enzyme has revealed that the active surface has two functionally and spatially separated sites: an "anionic" site attracting the quaternary nitrogen group of the ester by Coulomb and van der Waals forces, and an "esteratic" site which has an acidic and a nucleophilic group; the latter group forms a covalent bond with the electrophilic carbon of the carbonyl group (Fig. 2). The hydrolytic process takes part in two steps, as follows:





The enzyme is symbolized by the acidic group (H) and the nucleophilic group (G). In the first step the alcohol (choline) is eliminated by an electronic shift. As a result, an acetylated enzyme is formed. This acetylated enzyme reacts rapidly, in microseconds, with water to form acetate and restored enzyme (*10, 11*).

In the case of organophosphorus compounds a phosphorylated enzyme is formed which does not react with water, or reacts only very slowly, in days or weeks (*12*). For all practical purposes the enzyme is inhibited, and death of the animal ensues.

Once the mechanism of action was known, it seemed possible to reverse the reaction. A nucleophilic group should be able to displace the phosphoryl group from the nucleophilic group in the active site of the enzyme. Hydroxylamine was known, from Hestrin's experiments, to form hydroxamic acid from acetate in the presence of cholinesterase (*13*). It does this by attacking the carbon of the carbonyl group. Hydroxylamine indeed reactivates the phosphorylated enzyme, but it is a slow process, taking hours and requiring high concentrations (*12*). Wilson suggested the attachment of the active nucleophilic group to a quaternary nitrogen at proper atomic distance. This quaternary group should promote the interaction between reactivator and phosphorylated enzyme, just as acetylcholine is greatly superior to ethylacetate as a substrate, due to the attraction of the quaternary nitrogen group to the anionic site by Coulomb and van der Waals forces. Among a number of compounds suggested by Wilson and synthesized by Sara Ginsburg, pyridine-2-aldoxime methiodide (2-PAM) proved to be an extremely powerful reactivator (*14*). Kewitz *et al.* (*15*) applied the compound to mice and showed that it is an extremely potent antidote against insecticides and nerve gas poisoning, especially in combination with atropine. It is effective in animal experiments against 50 to 100 times the lethal doses (LD_{100}) of organophosphates. It has been successfully applied on a large scale, by Namba and Hiraki (*16*) in Japan, to human beings, victims of severe insecticide poisoning, and many lives have been saved. The extraordinary potency and reactivating power were surprising. Wilson (*17*) and his associates started, therefore, to explore the basis for this potency of PAM as a reactivator. They were able to demonstrate that PAM and phosphorylated esterase have molecular complementariness—that is, perfect fit; if the cationic nitrogen is attracted to the anionic site, the active oxygen atom is just one bond length away from the phosphorus atom.

Kewitz (*18*) has shown in animals treated with PAM that the compound acts by repairing the specific biochemical lesion produced by the organophosphorus compound—that is, by reactivating the phosphorylated enzyme in vivo. These observations were recently extended by Rosenberg (*19*) to the brains of intoxicated animals. The possibility of reactivating phosphorylated cholinesterase raised the question of whether electrical activity of a conducting membrane, after being irreversibly blocked by organophosphate, could be restored by the reactivation of the enzyme. Pyridine-2-aldoxime methiodide is unsuitable for such experiments, since it is lipid-insoluble and would not penetrate through the structural barrier. A lipid-soluble derivative of PAM, benzoyl pyridine oxime methiodide, which is a good reactivator of

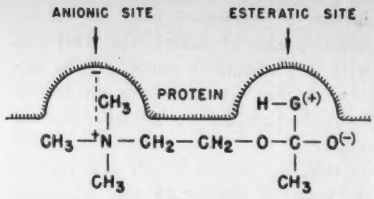


Fig. 2. Schematic presentation of the interaction of the active groups in the surface of cholinesterase and the substrate: the Michaelis-Menten complex. H represents the acidic group and G, the nucleophilic group, in the enzyme surface. [Nachmansohn and Wilson (*11*)]

phosphorylated enzyme and was synthesized by Sara Ginsburg, was used by Hinterbuchner (*20*). He exposed two preparations to an organophosphorus compound (paraoxon) until electrical activity was irreversibly blocked; this took from about 8 to 10 minutes. After that the control was washed with Ringer's solution. Activity was not restored. On washing the other preparation with benzoyl pyridine oxime, electrical activity reappeared. Thus, electrical activity, irreversibly blocked, has been restored by a specific chemical reaction—that is, by the removal of a phosphoryl group from the enzyme.

The Receptor Protein

I should like now to turn to another protein of the acetylcholine system, the receptor protein. Although a receptor for acetylcholine has long been postulated on a theoretical basis, experimental evidence for its existence was offered only several years ago in experiments with intact electroplax from the electric organs of electric fish. It was shown that acetylcholine and related compounds (such as, for instance, carbamylcholine, decamethonium, and procaine) in very low concentrations block electrical activity without affecting cholinesterase activity. Even concentrations 200 times as high as those required for block did not markedly affect the enzyme activity (*21*). Obviously, these compounds act on a similar but different cell constituent, the long-postulated receptor.

In tests of the effects of these compounds on the electrical characteristics, a striking difference became apparent: one type of compound blocked electrical activity with simultaneous depolarization; the second type blocked but did not depolarize the membrane. Depolarization implies, of course, increased con-

ductance, postulated to be the physiological function of acetylcholine. In general, acetylcholine and other methylated quaternary nitrogen derivatives blocked with depolarization, whereas tertiary analogues blocked but did not depolarize. Apparently, acetylcholine and other related compounds produce a change in the receptor resulting in a state of membrane conductance similar to the physiological one during electrical activity. The tertiary analogues combine with the active site but do not produce the change. In analogy with enzyme chemistry, we refer to the one type as receptor activators, to the other as receptor inhibitors.

The striking difference between quaternary compounds and their tertiary analogues appears particularly pertinent in the light of binding studies made with the enzymes cholinesterase and choline acetylase. If the binding of quaternary inhibitors (for example, tetramethylammonium and trimethyl ethanolamine) is compared to the binding of their tertiary analogues (trimethylammonium and dimethyl ethanolamine), the extra methyl group does not increase the binding (*22*). But the enzyme activity with the corresponding esters is greatly increased by the extra methyl group. The rate of acetyl enzyme formation increases tenfold. An analogous situation prevails with choline acetylase (*23*). How can we explain this remarkably powerful action of one methyl group on the enzymic process? A quaternary nitrogen group has a tetrahedral structure and is more or less spheric in shape. The extra methyl group is not in touch with the protein surface unless the protein changes its shape and envelops the quaternary group. Some support for the assumption of a change of configuration comes from observations on the entropy of activation of hydrolysis: that of the acetylcholine is very favorable as compared to that of the tertiary analogue. The difference due to the presence of the extra methyl group is about 25 to 30 entropy units (*24*). The problem is being investigated at present by Allen Gold. If the assumption is borne out, it may explain the trigger mechanism of the action of acetylcholine on the receptor protein. A small local folding of a helical or nonhelical section of a protein chain may remove a positively charged amino group from a strategically located point, thereby permitting the flow of ions through the membrane. A 2- to 4-angstrom shift of the charged group may be sufficient to account for the proposed trigger action. We know indeed that for one molecule of acetylcholine metabolized, about 1000 sodium ions may flow into the interior.

To study a protein by studying reactions on the intact cell is unsatisfactory. It appeared necessary to isolate the protein. The first notable attempt to isolate the receptor was made by Chagas (*25*) and his associates in Rio de Janeiro, and they deserve great credit for their initiative. They injected a radioactive curare-like compound, the triethiodide of gallamine, into electric tissue and prepared an extract which they dialized against distilled water. The compound appeared bound to components of the extract. But this binding could be due to Coulomb and van der Waals forces. Indeed, curare readily combines with all kinds of macromolecules rich in negative charges, such as acidic polysaccharides and nucleic acids (*26*). But the complex is readily dissociated by increasing ionic strength. It was therefore decided to try a different approach. Ehrenpreis (*26*) prepared extracts from electric tissue, fractionated them with ammonium sulfate, and tested the binding of curare to the proteins in equilibrium dialysis, according to the method of Klotz (*27*), against phosphate buffer at *p*H 7.5 and ionic strength 0.1. No binding of curare was observed when freshly prepared extract was used, but with a fraction obtained with ammonium sulfate at 60 percent of saturation, and a fourfold concentration, binding was obtained. Moreover, some of the protein was precipitated by curare. Most of the protein which could be precipitated by curare was in the fraction obtained with ammonium sulfate at 30 percent of saturation. When this protein was separated and dialyzed against phosphate buffer at *p*H 7.5 and ionic strength 0.1, part of the protein went into solution, but one part remained precipitated. This part could only be solubilized at a *p*H of 9. Curare has, in addition to the two quaternary nitrogen groups, two phenolic hydroxy groups. These groups dissociate at *p*H 9. Possibly they form hydrogen bonds with this particular protein. Urea dissociates the complex. This difference between the curare complex formed with this particular protein and that formed with other proteins and macromolecules is most fortunate because it permits separation of the protein in a relatively simple way and essentially as one component. According to ultracentrifuge and electrophoretic studies, 90 percent or more of the purified preparation is formed by this one protein. Its molecular weight is around 100,000 (*28*).

Now came the crucial question: How can we identify this protein and decide whether it is the acetylcholine receptor protein? Such a difficulty obviously does not arise in enzyme purification. At this point the availability of a monocellular preparation which had been developed with great resourcefulness and originality by Schoffeniels (*29*) became decisive for the identification of the protein as the physiological acetylcholine receptor.

Monocellular Electroplax

A single electroplax is dissected from the bundle of Sachs, the electric organ situated at the tail end of *Electrophorus*; there, the extracellular space separating the individual cells is large (Fig. 3). The electroplax is more or less rectangular in shape, varying between 5 and 15 millimeters in length, 1 and 1.5 millimeters in height, and 0.5 and 1.0 millimeter in thickness. The two opposite faces of the cell differ in function and structure: the caudal face is innervated and conducting, the opposite face is nonconducting and has many digitations, which greatly increase the surface. Each cell is located in a compartment formed by connective tissue. The technique requires complete removal of the connective tissue of the adjacent compartment situated close to the conducting membrane.

As shown in Fig. 4, the cell is kept between two nylon sheets, one with a window adjusted to the dimensions of the cell, the other with a grid consisting of nylon threads by which the cell is pressed against the window. The sheets are mounted between two blocks of Lucite (Fig. 5), each containing a pool. When the two blocks are fixed, the two pools of fluid are completely separated by the cell. Ions or other chemicals dissolved in the solution cannot pass from one side to the other except through the cell. The fluid of one pool bathes the conducting membrane, that of the other bathes the nonconducting membrane.

This unique preparation permits separate analysis of the properties of the two types of membrane. It is extraordinarily sensitive and versatile. Compounds that react with the acetylcholine system affect electrical activity in low concentrations; acetylcholine, for in-

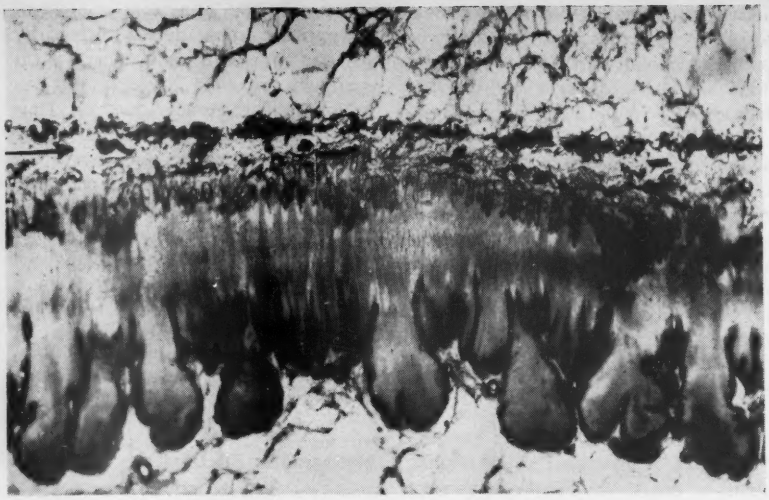


Fig. 3. Photomicrograph of a cross section of an electroplax from the bundle of Sachs of *Electrophorus*. Innervated membrane on the top, nonconducting membrane on the bottom. The arrow marks the space between the connective tissue of the adjacent department and the innervated membrane. The connective tissue must be removed by dissection. (About × 146) [Nachmansohn *et al.* (*41*)]

stance, blocks conduction reversibly at a concentration of $10^{-7}M$. The various electrical characteristics can be studied with intracellular electrodes. Figure 6 illustrates the difference between a receptor activator (carbamylcholine) and a receptor inhibitor (tetracaine) tested with this preparation. The former blocks the electrical activity, and simultaneously a depolarization takes place; with the latter, the resting potential remains unchanged when electrical activity ceases. Both of the effects are readily reversible. The preparation permits the correlation of electrical characteristics with chemical factors and with ion flux.

The availability of a suitable monocellular preparation eliminated many difficulties encountered with previous preparations and, in general, became decisive for further progress. In particular it made possible identification of the protein isolated and assumed to be the physiological acetylcholine receptor. When Ehrenpreis tested the binding strength of the isolated protein with respect to a great variety of tertiary and mono- and diquaternary compounds related in structure to acetylcholine, he found great differences. When Rosenberg and Higman tested the effects of the same series of compounds on the electrical activity of the monocellular electroplax preparation, a striking parallelism became apparent. With other proteins and macromolecules the binding, if it exists at all, is weak, and moreover, no parallelism exists between binding strength and effect on electrical activity. It seems, however, that a difference exists between receptor activators and receptor inhibitors insofar as the binding is concerned. Acetylcholine and other activators are bound to the receptor protein, but the binding seems to be in general poorer than that of receptor inhibitors, and poor as compared to the effectiveness on the activity of the electroplax. A similar phenomenon is encountered in enzyme chemistry. Inhibitors are frequently much more strongly bound than substrates. The dissociation constant of the neostigmine- or physostigmine-cholinesterase complex is 10^{-7}; that of acetylcholine, 10^{-4}. Even in the case of substrates, the strength of binding by no means parallels the rate of reaction with the enzyme. Acetylcholine, for instance, is much more poorly bound to cholinesterase than butyrylcholine is, but it is a 150-times better substrate.

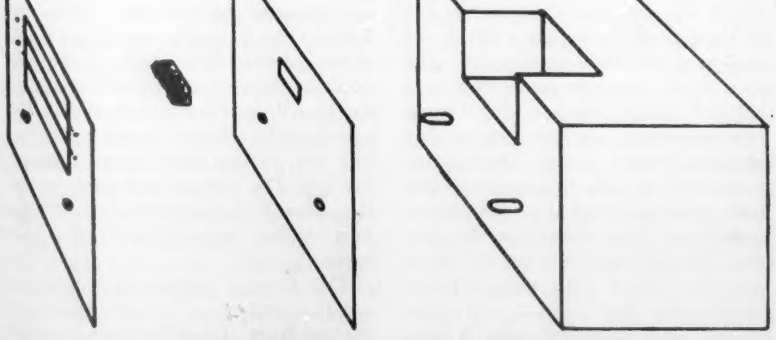


Fig. 4. Schematic diagram of the arrangement by which a single isolated electroplax separates two pools of fluid, showing the respective positions of one chamber for the pool of fluid, the sheet of nylon containing a window, the single electroplax, and the grid used for pressing the cell against the window. The other chamber is not shown (see Fig. 5). [Schoffeniels and Nachmansohn (*29*)]

Local Anesthetics and Curare

The properties of the protein in solution offer many interesting aspects. However, the reaction of this protein with local anesthetics, as observed both in the intact cell and in vitro, appears particularly pertinent. Local anesthetics such as procaine are strikingly related in structure to acetylcholine. In tetracaine one hydrogen atom on the N of the aniline is replaced by a butyl group. For many years it has been maintained that certain local anesthetics act by competing with acetylcholine for the active site of the receptor protein. Since they are receptor inhibitors, they act as antimetabolites, preventing acetylcholine from reacting with the active site. Some evidence for this assumption was offered with procaine on the monocellular electroplax (*29*). Recently, Rosenberg and Higman (*30*) compared the effectiveness of procaine, tetracaine, and dibucaine with respect to their effectiveness on the isolated single electroplax. They found tetracaine to be about 12 to 15 times as potent as procaine, and dibucaine twice as potent as tetracaine. When the binding strength of these three compounds with respect to the receptor protein was tested, a striking parallelism between binding strength and potency became

again apparent (*31*). The binding has a high degree of specificity.

Recently, Higman and Bartels (*32*) studied the competitive nature of the action of various receptor activators and inhibitors by testing the effects on the electrical characteristics with intracellular electrodes. They have accumulated a considerable amount of evidence for the competitive nature between the action of acetylcholine on the one hand and tetracaine and other receptor inhibitors on the other hand. For instance, a cell depolarized by acetylcholine is, even without removal of acetylcholine, completely repolarized by tetracaine or eserine as postulated by theory.

These results provide a chemical basis for the understanding of the action of certain local anesthetics. Moreover, since it is known that local anesthetics block electrical activity in all conducting fibers, the observations provide evidence that the acetylcholine receptor protein is present and essential for the generation of bioelectric currents in axons; this finding supplements the evidence previously obtained for the essentiality of acetylcholinesterase.

The strong binding of curare to the receptor protein has been discussed. The famous observation of Claude Bernard that curare acts only on the neuromuscular junction and does not affect conduction in nerve and muscle fibers formed for a long time the basis for the idea that there is a specific chemical mechanism at the junction. Some 15 years ago my associates and I offered experimental evidence that lipid-insoluble quaternary compounds cannot penetrate into the axon, apparently because of structural barriers (*33*). We proposed this as an explanation of why curare, acetylcholine, and other lipid-insoluble quaternary nitrogens do not affect conduction. Recently, Dettbarn (*34*) applied curare to the Ranvier nodes of a single isolated frog sciatic fiber, where, as we have seen, the axonal membrane is covered only by a thin and porous structure. He obtained rapid and reversible block of electrical activity. Walsh and Deal (*35*) treated desheathed frog sciatic fibers with a detergent, cetyltrimethyl ammonium bromide. After this treatment, curare, acetylcholine, neostigmine, and other quaternary compounds, inactive before, reversibly blocked electrical activity. A depolarizing action of acetylcholine was observed by Armett and Ritchie (*36*) on the desheathed cat vagus. Quite recently, Dettbarn and Davis (*37*) obtained a depolarization and a rapid and reversible block of electrical activity by acetylcholine applied to axons of somatic fibers of crustaceans. Finally, Rosenberg and Ehrenpreis (*38*) tried to reduce the structural barrier with enzymes. Among the great number of enzymes tested, cobra venom proved to be successful. After a 30-minute exposure of the giant axon of the squid to cobra venom (10 μg/ml), the venom was removed. The electrical activity was unimpaired. When curare was then applied, it rapidly and reversibly blocked electrical activity. Another venom, that of the cottonmouth moccasin, was found by Rosenberg (*39*) to be even more effective; after treatment with this venom, curare (in low concentrations) and acetylcholine blocked reversibly the electrical activity of the giant axon of the squid. In contrast, a series of tertiary nitrogen derivatives, related in structure to acetylcholine but lipid-soluble and show-

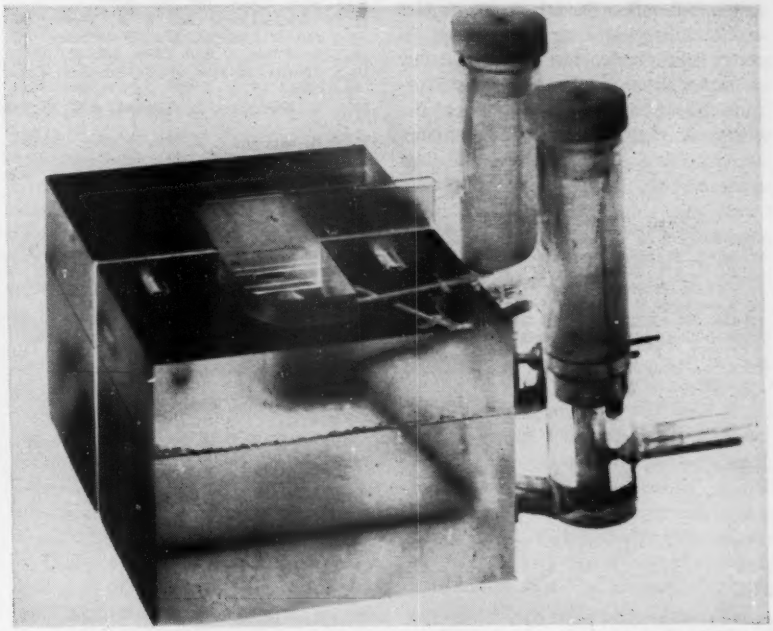


Fig. 5. Chamber with the two pools of fluid separated by the electroplax. At right are the air lifts for the two pools. [Schoffeniels (29)]

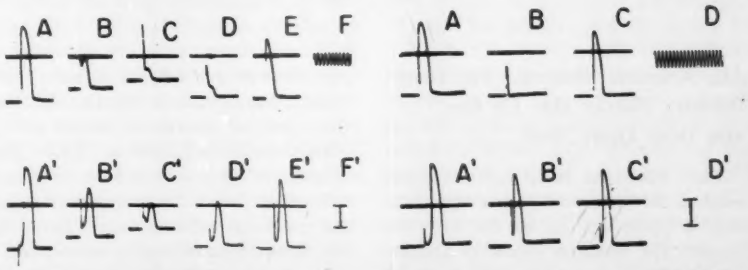


Fig. 6. Effects of a receptor activator (carbamylcholine) and of a receptor inhibitor (tetracaine) on the resting potential and the action current of a single isolated electroplax. The recordings were made with the cathode ray oscilloscope by means of microelectrodes, one of them intracellular. The value for the resting potential, measured by the distance between the two lines, is usually about 85 millivolts. There is overshoot during the discharge. (Left) *A–E*, direct stimulation; *A'–E'*, indirect stimulation; *A,A'*, control in Ringer's solution; *B,B'* and *C,C'*, at 1 and 4 minutes, respectively, after the addition of carbamylcholine ($5 \times 10^{-5}M$); (return to Ringer's solution at 5 minutes); *D,D'*, and *E,E'*, at 12 and 20 minutes, respectively. Calibration: *F*, 1000 cy/sec; *F'*, 50 millivolts. (Right) *A–C*, direct stimulation; *A'–C'*, indirect stimulation; *A,A'*, control in Ringer's solution; *B,B'*, at 5½ minutes after the addition of tetracaine ($5 \times 10^{-5}M$); (return to Ringer's solution at 6 minutes); *C,C'*, at 17 minutes (stimulus strength: *A'*, 30 volts; *B'*, 100 volts; *C'*, 60 volts). Calibration: *D*, 1000 cy/sec; *D'*, 50 millivolts. [Higman and Bartels (*32*)]

ing good and relatively specific binding to the receptor protein in solution, block conduction in the squid axon in concentrations surprisingly close to those previously observed on the synaptic junctions of electroplax.

Conclusion

The dramatic developments of biochemistry in the last few decades have greatly promoted our understanding of cellular function in terms of physics and chemistry, and we are reaching, in some fields, molecular levels. The few examples discussed in this article illustrate the approach to the analysis of the chemical factors that control nerve activity and the recent advances achieved (*40*).

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Science and the News

The Kefauver Hearings: The Drug Industry Finally Has Its Day and Does Quite Well

Last week the Kefauver committee entered its third, and presumably final, year of investigation of the drug industry. The hearings began in December 1959. Kefauver hopes to wind them up in the first few weeks of the new congressional session. What has taken so long is that Kefauver used most of the first two years for an intermittent but what must have been for the industry an excruciatingly prolonged exposé of what he saw as the industry's failure to properly serve the public interest.

Early last summer Kefauver produced a bill intended to reform the industry, and since then the hearings have been, technically at least, devoted to soliciting the views of interested parties on his "Drug industry antitrust bill." This "legislative" (as opposed to investigative) phase of the hearings began with the testimony of the American Medical Association in July, and reached a critical point last week with the testimony of the Pharmaceutical Manufacturers Association. Sandwiched in between was the testimony in September of Welfare Secretary Abraham Ribicoff, presenting the Administration's views. One of the curious aspects of all this testimony was that the drug industry's position turned out to be closer to the Administration's view than to that of its ally, the AMA.

Kefauver is asking for two quite different types of reform. The first half of his bill is concerned with amendments to the laws governing the Food and Drug Administration. In general approach, although not in detail, these amendments followed the recommendations of HEW, which are about the same now, under Ribicoff, as they were before the change in Administration. They would give FDA a stronger hand against makers of substandard drugs, require proof of efficacy as well as the presently required proof of safety before a new drug is allowed on the market, require the drug companies to provide wider distribution of information about new drugs, particularly regarding unfavorable side affects; and give the government authority over the choice of generic names for drugs.

Conflict

The AMA opposed all of these proposals, except the first, on which it took no position. Ribicoff supported, and the industry accepted, all of them, although not in the precise form Kefauver has suggested.

On generic names, for example, the AMA flatly opposed giving authority to the government, on the grounds that

a newly formed nongovernmental committee would serve to correct the abuse that is claimed to exist: a tendency of drug manufacturers to give drugs an unwieldy generic name and a catchy brand name, so encouraging the physician to prescribe by brand name instead of generic name. Ribicoff gave, as a horrible example of this, the case of a drug sold at $7 under the brand name Cortate. The same drug could be bought for $1 if the physician, instead of writing "Cortate" on his prescription blank, wrote "desoxycorticosterone acetate." But Ribicoff said he saw no need for his department to decide all generic names; he asked, instead, for standby authority for the government to step in only when the private committee, which includes representatives of the industry, could not agree on a reasonably simple name. The industry took the same position, and Kefauver appeared ready to accept this change.

Efficacy

On requiring proof of the efficacy as well as of the safety of a new drug, the AMA, again, was in flat opposition. It argued that FDA might interpret this to mean the right to pass on *relative* efficacy, and keep a drug off the market not on the grounds that it would not work, but on the grounds that it would not work as well as other products already on the market. No one has argued that FDA should have this power, partly because, unless a drug is exceptionally effective, it is impossible to reach a firm judgment on just how good it is until after it has been widely used, partly because even if one drug is better for most patients, a second drug is often better for some patients. FDA is already judging efficacy in most cases, on the grounds that if a drug has side effects, as almost all do, or if a drug is going to be used in connection with a life-threatening disease, a judgment on efficacy is a necessary part of judging safety.

The AMA therefore argued that the efficacy provision would be of no real value since it would only extend FDA's authority to harmless drugs to be used for non-life-threatening diseases, and very few of these drugs would be prescription drugs, which are the only kind affected by Kefauver's bill. This small advantage, in the AMA's view, was not worth the risk, however small, of the provision giving FDA power to judge relative efficacy.

Both the industry and Ribicoff, though, backed the efficacy provision, which is, by far, the most widely accepted of all the reforms urged by Kefauver. Ribicoff argued that it would not only close the small gap in the present law but would give the FDA power to prevent unfounded claims for a drug. As things are now, he said, FDA must approve a drug for sale so long as its good effects appear to outweigh its harmful effects; but since FDA has no direct authority to require proof of efficacy, it has no power to disapprove a drug merely because there is a lack of evidence to show that it is as good as its manufacturer claims it is. Ribicoff said that under the present law, FDA must occasionally approve a new drug application with the knowledge that the manufacturer is going to promote it with unsubstantiated claims. FDA must wait for the drug to go on the market and then bring a court action in which the burden of proof is on the government to show that the drug will not do as much as its manufacturer claims, rather than on the manufacturer to show that it will do what is claimed. The industry, in contrast to the AMA, accepted the efficacy provision, insisting only that it be understood that the manufacturer need show only "substantial" rather than definitive proof of his claims. Kefauver said this was all the law would require.

The discussion of other points in the first half of the law was similarly cordial. Neither side was giving in on anything on which it stood any significant chance of winning anyway. The drug industry, for example, had no occasion to follow the lead of the AMA and oppose the wider dissemination of detailed information on drugs since the FDA had already settled the question by putting through a set of new regulations, under its already existing powers, which made Kefauver's provisions superfluous. The AMA had argued that its own newly reorganized information program (a department in the *AMA Journal* and an expanded yearbook) would give the doctor all the information he needs, and that the Kefauver proposal would just fill up the doctor's wastebasket. On proof of efficacy as well as safety, the industry's choice of position, again, was not too difficult to reach: there was not only a great deal of support for this within the medical profession, despite the AMA position, but as a practical matter it is hard to explain to the public or to a congressman why it is unreasonable to expect a manufacturer to have reasonable proof that a drug will do what it is claimed to do. The AMA had not been able to offer an explanation of how the provision could be interpreted to give FDA power to keep a useful drug off the market merely because it seemed not as useful as another drug. The AMA's reasoning, apart from a disinclination to give the government any greater control than it now has over the medical profession, appeared to be that even a comparatively worthless drug sold through exaggerated claims might turn out to be surprisingly valuable and that it would, therefore, be best, providing the drug met the safety test, to allow wide latitude. But if the AMA's information program was going to be as effective as it was promised to be, it would be difficult to see how a drug promoted through unsupported claims would get the wide use that would turn up its surprising value.

Patents

Where the industry and Kefauver sharply parted company was on the second half of the bill, which was aimed at restricting patent rights in the drug industry. This was the part of the bill that was closest to Kefauver's heart, but he clearly took a beating, and at the end of the hearing he in effect conceded what had already become obvious: that the patent law changes he was asking stood no chance of getting through Congress.

The first half of the bill contained reforms which had been urged for years. In 1950, for example, the AMA's own council on drugs had recommended that the efficacy test be added to the law. The reforms have very little to do with the antitrust and monopoly problems that the Kefauver committee was authorized to study. If he had cared to, Senator Hill, chairman of the Labor and Welfare committee, could have claimed jurisdiction and kept Kefauver from dealing with these reforms at all. Kefauver's special interest and his own ideas appear in the patent section of the bill, where he proposed to bring down the price of drugs by removing much of the perfectly legal monopoly powers which the major companies hold through their patents. Curiously, the reason this approach was so promising was the very fact that the drug industry is one of the least monopolistic of large industries. Twenty-two companies are classed as major, 140 are substantial enough to belong to

the Pharmaceutical Manufacturer's Association, and there are more than a thousand lesser companies. Kefauver proposed that a drug manufacturer be required to license any of his competitors to produce a patented drug after three years. He also wanted to bar patents for molecular modifications—minor changes in a known drug which will produce a patentable variation—unless the variation were proved superior to its predecessor.

In this way, Kefauver felt, the high profit margins the manufacturers were enjoying on many drugs would be forced down by the loss of the patent monopoly. He argued that the three years of normal patent protection plus royalties on all sales of the drug for the remaining 14 years of the patent protection, when compulsory licensing would be in effect, would give the companies all they needed to enable them to recover the heavy investment in research and testing usually needed before a useful new drug was produced. He argued that the second patent provision, prohibiting protection for minor variations of known drugs, would complete the job by removing the incentive for the industry to aim much of its research at producing patentable variations of known drugs at the expense of concentrating fully on producing new drugs of the most benefit to the public. As a result, he believed, even though the first provision might lead to less spending on research, the second would offset this loss by assuring that the money that was spent would be spent in a more productive way.

Doubts

There is little doubt that Kefauver's patent limitations would indeed force down the price of drugs. Where Kefauver ran into serious difficulty was on the question of what else they might do. All of Kefauver's proposals are intended to have an effect on the price of drugs. The provision in the first part of the bill giving FDA a stronger hand against the makers of sub-standard drugs, for example, will, Kefauver hopes, make physicians more willing to prescribe by generic name instead of trade name. More active FDA supervision of manufacturers, Kefauver believes, will tend to lessen the feeling among physicians that in order to assure that their patients get first-quality drugs it is best to specify the trade name of a manufacturer of known reputation. In fact, the effect may be just the opposite, for although the great majority of unbranded prescriptions are just as good as those sold under well-known trade names, the more active FDA is in taking action against substandard drugs, the more often physicians will be reminded that there is at least a slightly greater chance that their patients will get a substandard product if they fail to specify a known trade name. It is perfectly possible that the effect of this reform will be both to make it even safer than it is now to prescribe by generic name and at the same time to make physicians even more wary of doing so.

This typifies the difference between the proposals in the two parts of the bill: in the first half, you have widely supported, long-discussed reforms which may or may not have a significant effect regarding Kefauver's special interest in lowering the cost of drugs. In the second half of the bill, you have provisions which will have a direct effect on drug prices, but which may or may not have good effects on the overall performance of the industry. In the first instance, pressure is on those who oppose the reforms to show what is wrong with them; in the second instance, those who oppose the reforms have only to raise a reasonable doubt about the wisdom of the proposal and they will have assured that the most Congress will do will be to say, "Let's look into this thing more carefully before rushing ahead." This is what the industry did very well.

Kefauver, for example, had assembled a good deal of data on the discovery of important new drugs in countries with varying degrees of patent protection. He interpreted the data to show that his proposals would not lead to a reduction in the number of important new discoveries even though they were likely to reduce the total overall number of new discoveries. The industry was able to offer an alternate interpretation of the same data which suggested just the opposite. This was all the industry had to do. Its interpretation was not convincing enough to thoroughly refute Kefauver, but it was convincing enough to raise doubts that Kefauver was right. On point after point, the industry was able to raise similar doubts, and sometimes quite convincing ones. Kefauver had not been proved wrong but as for his immediate chances of getting his patent proposals enacted into law, he might as well have been proved wrong.—H.M.

Population Boom: Administration Presents a Policy Statement That Is Ingeniously Confusing

In a speech that received surprisingly little attention, the Administration recently set forth its policy on the "population explosion" in lesser-developed countries.

The speech contained the Administration's first comprehensive statement on this politically sensitive subject. As is the style in virtually all official pronouncements that touch on birth control, bones were available for the watchdogs of all partisans. Behind the cautious verbiage and qualifications, however, was an acknowledgment that the Kennedy Administration desires to come to grips with the population problem.

Since the attitude of its predecessor was strict aloofness, the distance traveled to date by the Administration is relatively considerable. It has publicly exhumed the subject and has deemed it respectable for public discussion by government officials. It publicly acknowledges, in addition, that it has gone to the extent of helping some lesser-developed nations survey their population problems. Such surveys must inevitably precede any attempt to develop a population control program. And some officials say privately that in a few countries, U.S. assistance has gone beyond the census-taking stage.

Assistance Offered

The speech setting forth the U.S. position on population control was delivered 30 November in Washington by William T. Nunley, special assistant to Under Secretary of State George W. Ball. Nunley spoke at the National Conference for International Economic and Social Development, which comprises several hundred organizations and individuals supporting U.S. foreign aid efforts. He described his speech as an officially approved statement.

Sentiments favorable to U.S. assistance for population control predominated in his audience, and what Nunley had to offer was denounced as evasive by several persons present. In many respects it unquestionably was evasive, but strewn here and there through its five pages were some of the most remarkably frank public statements ever issued by a U.S. official on the subject of population control.

Nunley pointed out in the course of

his address that the State Department is "thinking about population problems and talking about them." This may seem a modest claim, but it is a marked departure from the situation that prevailed in the previous Administration and that for a short time was carried on by the current Administration. Eisenhower's attitude was summed up when he said in relation to population control assistance: "I cannot imagine anything more emphatically a subject that is not a proper political or governmental activity or function or responsibility." Taking their cue from the Chief Executive, Eisenhower Administration officials rarely referred to the subject. In the early days of the current Administration, the taboo remained in force until President Kennedy publicly referred on several occasions to his concern about the problem. It then became safe to talk about it publicly, and the existence of a population problem has been stressed with increasing frequency in the speeches of Kennedy's officials.

Nunley seemed for a moment to be announcing that the United States will directly assist other governments that seek our aid in population control: "Finally, we are prepared to consider on their merits certain types of requests for assistance to other governments. In fact, we have already begun to advise and assist a few governments in their efforts to acquire additional knowledge about their own population problems, specifically in the conduct of censuses."

Policy having been brought to this point, it was promptly enveloped in an obfuscating swarm of words, and on the basis of the text as a whole it would be impossible to say just what the United States is prepared to do about the population problems of lesser-developed nations.

The seeming decision to offer assistance would appear to have been set aside by the following: "I do not know whether or not the United States government will ever consciously provide specific assistance in controlling population growth, and I am even less certain whether we will ever offer assistance in support of birth control programs. At the present moment, incredible as it may seem to some Americans, birth control is not a major issue in most parts of the world. It certainly is not a policy objective of the United States Government."

The speech undoubtedly deserves a place in the archives of confusion, but since its subject is one on which official evasiveness has generally been the keynote, it commands attention. Most notably, it did not shut the door to U.S. assistance in population control efforts, and, on balance, it seemed to be saying such assistance may be forthcoming.

In response to inquiries on the provocative statement that "we are prepared to consider on their merits certain types of requests. . . . " the State Department said: "We are not closing the door to anything. We will consider any request for help and decide whether it is suitable."

Privately, however, it was stated that the Administration is determined to move in this area and is cautiously testing the political terrain. In that context, this ingeniously confusing speech makes considerably more sense.—D.S.G.

Civil Defense: Like It or Not, Believe in It or Not, the Program Will Soon Be a Reality

While debate continues on what type, if any, civil defense program the United States should adopt, the program selected by the Administration is rapidly becoming a part of the American landscape. The confusion that has attended the effort—especially on the question of private versus community shelters—has obscured the managerial achievements involved in putting together a program and bringing it into being.

Civil defense has been a policy objective of the United States for over a decade, but after having labeled it as such, both the Truman and Eisenhower administrations left it to languish with small appropriations, inadequate leadership, and poorly defined goals. As a result, it took on an aura of unreality, and few citizens came to feel that it had a bearing on their lives.

In the past 4 months, however, the Administration has set clear goals—they are relatively modest—and put the program in the hands of effective managers backed by ample funds. Whatever the program's merits and implications may be, civil defense for the first time will soon be a functioning, visible undertaking that will make its presence felt in the lives of virtually every American.

Amid the debate over what should be done, it is therefore meaningful to survey the considerable amount that has already been done and determine how it was done.

The most significant administrative step involved the movement of the civil defense effort from the Executive Office staff of the President to the Department of Defense. The resources of the department, which is the best-financed, biggest, and most geographically widespread in the government, gave the civil defense program a powerful operating base which it previously lacked.

At the same time, Kennedy spoke out openly and repeatedly in behalf of civil defense, far in excess of anything done by his two immediate predecessors. The program was developed and put into operation against a background of an international crisis created by the Soviet resumption of nuclear testing, the walling off of East Berlin, and communist incursions in the Far East.

The civil defense program that Kennedy presented to Congress was clearly limited to attainable goals. In this respect it differed from earlier efforts which were enmeshed in a variety of concepts, many of them fuzzy and conflicting. The program, he stressed, was to be regarded as insurance against "an irrational attack, a miscalculation, an accidental war which cannot be either foreseen or deterred." He acknowledged that "it cannot give an assurance of blast protection that will be proof against surprise attack or guaranteed against obsolescence or destruction. And," he added, "it cannot deter a nuclear attack."

The program, as it was broadly outlined before Congress, was to be built around existing structures which would offer protection against fallout. In addition, steps would be taken to stockpile supplies and expand warning and training measures. The raging controversy over private and community efforts, incidentally, was touched off by Kennedy's observation that "financial participation will also be required from state and local governments and from private citizens . . . every American citizen and his community must decide for themselves whether this form of survival insurance justifies the expenditure of effort, time, and money." Subsequent references to individual efforts, coupled with the rapid growth of the fallout-shelter business and do-it-yourself articles in popular publications, tended to obscure the fact that the community shelter program was primary in the Administration's planning.

The political liability inherent in a shelter program that can be interpreted as offering protection for the rich and fallout for the poor has since caused Kennedy to limit his public statements to an emphasis on community facilities. Meanwhile, civil defense officials have no desire to dampen whatever individual efforts may be underway, and from time to time, they publicly state that private shelters have a place, too.

The private effort, despite the noise that accompanies it, has shown no signs to date of providing any significant amount of shelter space. The program for community facilities, however, is moving along at an extremely rapid pace, and it is the one that is going to bring civil defense into American life.

The Pentagon has announced that on the basis of pilot surveys, it expects to have located by next June shelter space in existing structures for some 50 million persons. Not long after that, it plans to have these spaces marked and stocked with rations for 2 weeks. In addition, it is in the process of arranging training for persons who will be assigned to supervise the shelters.

With these shelters providing space for something over 25 percent of the population, the Administration plans to ask Congress next year for funds to help communities build additional shelter space on a matching-fund basis. A program that will further bring civil defense into everyday life calls for providing a 16-hour medical self-help course for at least one member in every family. The course, developed by the Public Health Service in consultation with the American Medical Association, will be offered by committees which the Defense Department says have already been set up in most states.

The current federal budget for civil defense is slightly over $300 million. In the forthcoming Congress, the Defense Department is expected to receive at least double this amount, and it is reported that present plans call for spending a total of $5 billion over the next 5 years.

Confusion and controversy will inevitably accompany the development of the program, but it must be noted that in a remarkably short time civil defense has adopted a workable program, and whatever protection it may offer and whatever effect it may have on the American public, it will soon be here.—D.S.G.

Air Pollution: Auto Industry Bows to Ultimatum

The automobile industry, under pressure from Congress and the Department of Health, Education, and Welfare, last week announced plans to make so-called blow-by devices standard equipment, starting with the 1963 models.

The industry, which has become increasingly sensitive to the attention it is receiving from social critics and public health and safety authorities, came to the decision reluctantly. It had earlier made it clear that it felt it was the victim of some erroneous conclusions about the industry's contribution to air pollution.

The blow-by device is basically a tube which carries unburned hydrocarbons from the crankcase breather back to the intake manifold, where they are reintroduced into the engine and burned. The industry announced 2 years ago that it had found that some 30 percent of automotive pollutants—in the form of unburned gasoline—are emitted into the atmosphere through the crankcase breather. It immediately found itself beset by demands from public health authorities for factory installation of the device. The industry responded that the device would prove useful in California, because of atmospheric conditions there, but rejected demands for standard installation.

Last fall, the Department of Health, Education, and Welfare handed the industry an ultimatum calling for factory installation on all models by 1963. At the same time, warnings were received from Congress that legislation would be introduced making the device mandatory if the industry did not respond voluntarily.

Announcements

Coastal research workers are invited to submit material for inclusion in the recently established **Coastal Research Notes**, an interdisciplinary newsletter covering plans and projects in the field. The series will include items on future research, work in progress, field trips, new instrumentation, and cooperation between scientists in various fields. Deadline for inclusion in the first issue: *1 January 1962*. (William F. Tanner, Geology Department, Florida State University, Tallahassee)

Researchers concerned with **cognition and creativity in children** are invited to submit inquiries to the Galton Institute. The organization is planning research programs to devise suitable instruments for measuring, at the preschool level, those traits most frequently associated with creativity in adults. (Frieda B. Libaw, Galton Institute, 10400 Wilshire Blvd., Los Angeles 24)

A catalog of **alkaloid-bearing plants** has been published by the U.S. Department of Agriculture. The 287-page book (technical bulletin No. 1234) lists the family, genus, and species of all known alkaloid plants; the specific plant part in which the alkaloid exists; and the name of the alkaloids with their chemical formula. (Government Printing Office, Washington 25, D.C. $1)

Grants, Fellowships, and Awards

Grants-in-aid of **scientific research** —including the mathematical, physical, biological, and social sciences—are available from the American Academy of Arts and Sciences. The awards range from $500 to $1500. Deadline: *1 February 1962*. (Chairman, Committees on Research Funds, American Academy of Arts and Sciences, 280 Newton St., Boston 46, Mass.)

Guggenheim fellowships are currently available for graduate study in **rockets, jet propulsion, space flight**, and **flight structures**. Candidates must be residents of the United States or Canada and must plan to follow astronautics, rockets, or flight structures as a career. Recipients will study at the Guggenheim Jet Propulsion Center at the California Institute of Technology, the Guggenheim Laboratories for the Aerospace Propulsion Sciences at Princeton, or the Institute of Flight Structures at Columbia University. Fellowships provide full tuition and stipends up to $2000. Deadline: *1 March 1962*. (Guggenheim Foundation, 120 Broadway, New York 5)

Fellowships, scholarships, and assistantships in **forestry** are available for the 1962–63 academic year at Yale. Fellowships carry stipends up to $2900, scholarships cover tuition costs, and assistantships pay from $840 to $1800. Deadline: *1 February 1962*. (Yale School of Forestry, 205 Prospect St., New Haven 11, Conn.)

Applications are being received for the 1962–63 Sigma Delta Epsilon grant-in-aid to **women in science**. The award, presented by the Graduate Women's Scientific Fraternity, is available to any woman who holds a degree and has demonstrated outstanding ability in one of the mathematical, physical, or biological sciences. Preference will be shown to applicants 35 years of age or older. The $500 stipend may be applied either directly to the research project or to relevant course work. Deadline: *1 February 1962*. (Erma S. Vanderzant, Dept. of Biochemistry and Nutrition, Texas A&M College, College Station)

Applications are being accepted for the Edwin Leigh Newcomb awards in **pharmacognosy**. Three awards of $250 each will be presented, on the basis of essays or published papers, to an undergraduate student; a graduate student; and a teacher, research worker, or industrial scientist. Papers must contain some new information ascertained from studies made by the contestant, and must be principally within the fields of morphologic, taxonomic, physiologic, cytogenetic, or commercial pharmacognosy; or in drug plant cultivation. Phytochemical aspects of the work may be included in conjunction with one or more of the previously mentioned fields. Deadline: *1 February 1962*. (H. W. Youngken, Massachusetts College of Pharmacy, 179 Longwood Ave., Boston 15)

Scientists in the News

Biological Abstracts has announced the following appointments:

Phyllis V. Parkins, assistant director for editorial affairs.

Robert R. Gulick, assistant director for administrative and business affairs.

William C. Hoida, research coordinator.

Recent awards of the American Chemical Society:

J. R. Partington, professor emeritus of Queen Mary College in London, received the 6th annual Dexter award for his work in the history of chemistry.

Melvin Mooney, retired U.S. Rubber Company scientist, will receive the 1962 Charles Goodyear medal for his development of the Mooney viscometer and for his work on the physics of rubber.

Seibert Q. Duntley, research physicist and director of the visibility laboratory of the University of California's Scripps Institution of Oceanography, has received the 1961 Frederic Ives Medal of the Optical Society of America.

Harold Mayfield, of Toledo, Ohio, has received the Brewster memorial award of the American Ornithologists' Union for his 1960 monograph, *The Kirtland's Warbler*.

P. S. Gill, director of the Gulmarg Cosmic Ray Research Laboratory in Kashmir, India, and head of the physics department at the University of Aligarh, has been appointed 1961–62 visiting professor of physics at Washington State University.

Edward L. Criscuolo, a technologist in industrial radiography at the U.S. Naval Ordnance Laboratory, has received the 1961 Coolidge award of the Society of Nondestructive Testing for his work in industrial x-ray.

Lysle H. Peterson, professor of physiology at the University of Pennsylvania School of Medicine, has been named the first director of the university's Bockus Research Institute.

E. F. Knipling, director of the U.S. Department of Agriculture's entomology research division in Beltsville, Md., has won the first distinguished service award of Ford Farming magazine and the 1961 John Scott award of the Entomological Society of America. Knipling shared the Scott award with **R. C. Bushland**, livestock insects investigations leader in the USDA's entomology division at Kerrville, Texas.

Robert H. Luce has resigned after serving 17 years as head of biology at Rensselaer Polytechnic Institute. He will continue as a professor in the department. **Roland Walker**, professor of biology, has been named acting chairman of the department.

Julius London, associate professor of meteorology at New York University, has been named professor of astrogeophysics at the University of Colorado.

Wolf Vishniac, associate professor of microbiology at Yale University, has been appointed professor of biology at the University of Rochester (N.Y.).

Recent Deaths

Charles L. Crockett, 63; chief chemist for the Norfolk and Western Railway since 1946; 28 Nov.

Frederick C. Fishback, 63; surgeon and clinical associate professor of surgery at Georgetown University; 23 Nov.

Walter G. Flood; independent metallurgy consultant in Washington, D.C.; 27 Nov.

George Halperin, 80; physician and editor of the medical abstract section of the *Journal of the American Medical Association*; 7 Nov.

William A. Hamor, 74; retired senior director of research at the Mellon Institute; 23 Nov.

Horace J. Harper, 65; soils specialist at Ataturk University in Erzarum, Turkey, for the International Cooperation Administration, and former professor of soils at Oklahoma State University for 36 years; 8 Nov.

A. Langseth, 66; professor of chemistry at the University of Copenhagen; 20 Oct.

Horace N. Lee, 71; retired research microscopist and wood and paper technologist; 12 Oct.

Peter Payson, 63; assistant director of research for Crucible Steel Company in Pittsburgh, Pa.; 26 Nov.

Francis B. Stewart, 63; chemist with the Chemical Warfare Service in Battle Creek, Mich.; 27 Nov.

Clyde C. Taylor, 49; fishery biologist at the U.S. Bureau of Commercial Fisheries' biological laboratory in La Jolla, Calif.; 9 Nov.

Victor Tinderholt, 39; *Drosophila* geneticist with the City of Hope Medical Center's department of genetics in Duarte, Calif.; 21 Nov.

Joseph E. Willetts, 101; ophthalmologist and founder of the Eye, Ear, Nose, and Throat Hospital in Pittsburgh, Pa.; 27 Nov.

Erratum: In the announcement of the scholarships at German Institutions [*Science* **134**, 462 (18 Aug. 1961)], the address for the Humboldt Foundation was listed incorrectly. The address should have been Alexander von Humboldt Stiftung, Nassestrasse 11a, Bonn, Germany.

Erratum: In the report, "Cytogenetic behavior of a knobbed chromosome 10 in maize," by G. Y. Kikudome [*Science* **134**, 1006 (6 Oct. 1961)], two errors occur in the counts for family 61:36 for the *R:r* ratio in Table 1 (line 2, columns 2 and 4). The number of *R* kernels is 1338, not 1388; the total number of *R* and *r* kernels is 2718, not 2178.

Erratum: In the announcement on iodine-125 [*Science* **134**, 1605 (17 Nov. 1961)], Oak Ridge National Laboratory was erroneously reported to be producing the isotope for $1 per millicurie. The Atomic Energy Commission has not authorized a change in the laboratory's price of iodine-125, which remains at $15 per millicurie.

Book Reviews

Blossoms of 100 Flowers in Soviet Genetics

Some Problems of Evolutionary Genetics and Darwinism. Yu. M. Olenov. U.S.S.R. Academy of Sciences, Moscow, 1961 (in Russian). 163 pp. 83 kop.

Communication between biologists of the East and West appears to be increasing apace. English translations of Russian periodicals are appearing with greater frequency in our libraries. In turn, our Russian colleagues are becoming more closely acquainted with what is being accomplished in the laboratories of the Western world, especially in fields which have been recently dormant or undeveloped in the Soviet Union. In the area of genetics and evolution, the 1948 party line is no longer binding, and Mao's hundred flowers are apparently encouraged to blossom. This policy obviously requires that information in many hitherto neglected areas be supplied to Soviet research workers. Indeed, as may be learned from the volume under review, texts by Brachet, by A. J. Cain, by Villee, and by Wagner and Mitchell have recently been published in Russian-language editions. Olenov's book itself is in the main directed toward bringing the reader abreast of the times in several important areas. It consists of five essays. The first two comprise a chapter headed "On the material basis of heredity." The remaining three, organized in two chapters, deal with speciation and several other questions of broad evolutionary significance.

The 90 pages of the first chapter provide a comprehensive, up-to-date review of a number of aspects of molecular biology, including such topics as the self-reproduction and synthesis of deoxyribonucleic acid and ribonucleic acid, the basis of antibody formation, the complex nature of genes and genetic regions, the various peculiarities of the hereditary apparatus of bacteria, the epigenetic systems in cellular differentiation, and the like. That the purpose of this section is didactic and that molecular genetics is new to the U.S.S.R. is testified to by the fact that, out of some 350 bibliographic citations, 90 percent are of non-Russian origin. Of the 32 Russian references, 24 are dated 1958 or later. For that matter, some 90 percent of the foreign material quoted has been published, as might be expected, within the last decade.

The remainder of the book seems entirely unrelated to the first chapter, and the bibliography pertaining to the two essays in that chapter in no way overlaps with the more than 200 references cited in the concluding three. Here the proportion of Russian material runs to nearly a quarter of the total, but it may be worth noting that close to 70 percent of the foreign citations, contrasted with 20 percent of the Russian ones, are of 1951 or later vintages.

The main conclusion of the first two essays in the second section affirms the primacy of natural selection as an evolutionary force. Random drift is viewed as unproven and of unlikely significance, while geographical isolation is adjudged to be only an ancillary process to selection. In the course of developing these theses, much current literature is reviewed. The argumentation is always carried on within the framework of genetic and evolutionary evidence, and the discussion is at a high level of sophistication. Whether or not one agrees with the deductions reached, the author wins respect for his fair statement of the issues and the evidence.

The final essay deals with the question of whether or not organic evolution is a progressive process. The discourse is vaguer and less data-based than in the earlier parts, but even here the guidelines are more biological than philosophical.

The overall impression of this book is a very favorable one. It originated in the Soviet Academy's Institute of Cytology, and the contrast in this institution's scientific level and methods of presenting ideas compared with those to be found in the publications of such a sister organization as the Institute of Genetics is refreshing. One would seek in vain in the present work (except for two lapses in citing a nonbiological authority) for the earmarks of dogma so universally found when Russian genetics lived in the penumbra of late-model Stalinism. In fact, instead of judging the validity of data by their canonical conformity, a characteristic of many biological debates of that era, there is an attempt here to bolster Darwin's own authority by appeal to modern data!

Whatever disagreement, with either details or the author's main conclusions, there may be, this work can only be saluted as one of the recent significant signs of the rebirth of Soviet genetics. It serves admirably to inform our Soviet colleagues of the developments in many areas of molecular genetics, which came to fruition while they were *hors-de-combat.*

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Psychopathology

The Myth of Mental Illness. Thomas S. Szasz. Harper, New York, 1961. xiii +337 pp. $7.50.

Thomas Szasz's volume is enormously courageous and highly informative, and it makes fascinating reading for anyone with a serious interest in the problem of psychopathology. But it is a difficult book to review, because it involves a number of strong, more or less independent "themes" rather than a single sustained argument. Thus, in order to avoid quite serious logical complications but at the same time retain the sense of vitality which the book unquestionably has, I propose to examine it here, so to say, thematically, rather than as an organic whole.

"I submit that the traditional definition of psychiatry, which is still in vogue, places it alongside such things as alchemy and astrology, and commits it to the category of pseudo science" (page 1).

Coming as they do from the pen of

a distinguished professor of psychiatry (at the Upstate Medical Center of the State University of New York, in Syracuse), this and related statements set the tone of candor and criticism that prevails throughout. In the concluding chapter we read, in like vein:

"It is customary to define psychiatry as a medical specialty concerned with the study, diagnosis, and treatment of mental illness. This is a worthless and misleading definition. Mental illness is a myth" (page 296).

Quickly, then, we pick up a second theme, or objective: "to redefine the problem of mental illness so that it may be encompassed under the general category of the science of man." Szasz is well prepared for such a large enterprise; for in addition to his basic training in medicine and psychoanalysis, he also shows himself conversant with the social sciences and with the history of medicine, philosophy, literature, and political theory.

Conceived in such a broad context, mental illness is seen as more a mode of "communication" than as an illness or disease in the proper medical sense of these terms. And this emphasis permits the author to identify conversion hysteria as the prototype for all forms of personality disorder, since it (and they) effectively translates "problems of living" over into the language of the body, thus giving only the *appearance* of genuine illness. Therefore, so-called mental illness is a "myth."

But the mythical emphasis is, in one way, overextended: it does not do justice to the reality of the suffering which is here involved or to the legitimacy of such suffering, considered in a moral and social context.

This oversight is all the more remarkable when it is realized that, in later parts of his book, Szasz devotes many well-reasoned pages to the necessity for social (moral) rules and the human necessity for rule-following. The book reaches its lowest point of coherence, from my point of view, when Szasz suggests that mental illness consists of an individual's being somewhat confused about the real rules of "the game" and "playing" according to distorted or idiosyncratic ones. This book would have a far greater over-all cogency if it concluded on the note that the "sick" person knows quite well what the rules are and that he sickens, not because of playing the wrong "game," but from *not* playing the game which he knows perfectly well to be the right one. In other words, the basic problem would thus be "evil" rather than mere ignorance.

In short, then, the author is eminently bold and often brilliant in his devaluation of current psychiatric theory and practice, but he falls short of attaining a fully consistent and powerful alternative. As a *try*, it is decidedly in the right direction.

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Early Mathematics

Science Awakening. B. L. Van der Waerden. Translated by Arnold Dresden. Oxford University Press, New York, 1961. 306 pp. Illus. $7.50.

For an earlier generation of graduate students, Van der Waerden's *Algebra* was virtually a household phrase; more recently the author's name has been recalled in connection with a scholarly and beautiful book on ancient mathematics. His *Ontwakende Wetenschap* (1950) was welcomed with justifiable enthusiasm [see *Mathematical Reviews* **12**, 381 (1951)], and the richly illustrated English version, *Science Awakening*, which appeared in Holland in 1954, was also warmly received [see *Scientific Monthly* **80**, 377 (1955)]. The format, illustrations, and text of the 1954 translation are virtually unchanged in this American printing (1961), and the title page makes no reference to the earlier version; but, in a revised "Preface to the English edition," the author refers to the present work as "the second English edition." There are, to be sure, a few changes in the exposition. On pages 73 and 79, for example, one finds new interpretations of two Babylonian problems; and on page 277 the modified description of Heron's *Metrics* no longer stigmatizes it as "a very childish little book." Nevertheless, these revisions do not substantially alter the sound judgments made almost a dozen years earlier. The book remains a model of historical-mindedness, a model in which opinions are independently arrived at from a critical reading of the best sources and authorities. The author, for instance, makes use of Neugebauer's recent valuable research on the role of Babylonian methods in the development of Greek mathematics; but whereas Neugebauer concluded that "the traditional stories of discoveries made by Thales or Pythagoras must be discarded as totally unhistorical" (*The Exact Sciences in Antiquity*, Brown University Press, Providence, R.I., ed. 2, 1957, page 148), Van der Waerden argues (page 89) that this research "knocks out every reason for refusing Thales credit for the proofs and for the strictly logical structure which Eudemus evidently attributes to him." Here and there a reader may question a bold conjecture made by the author. Were the "inner causes" of the "decay of Greek mathematics" really the difficulty of geometric algebra and the difficulty of the written tradition (pages 264–266)? Not necessarily; but then, one of the virtues of this book is that Van der Waerden distinguishes clearly between the historical evidence and the thought-provoking conclusions that he has drawn therefrom.

Science Awakening is as attractively printed as it is accurately written, and only the title is infelicitous. The work is a clearly circumscribed and well-ordered history of pre-Hellenic and Greek mathematics; and while mathematics may be a handmaiden of the sciences, it is not itself—at least in the usual sense of the word—one of the sciences.

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Comprehensive Résumé

The Cell. vol. 2, *Cells and Their Component Parts*. Jean Brachet and Alfred E. Mirsky, Eds. Academic Press, New York, 1961. xiv + 916 pp. Illus. $25.

This comprehensive treatment of cells and their component parts is volume 2 of a series evidently designed as a modern counterpart of E. B. Wilson's classic but now outdated *Cell in Development and Heredity*. The topics included in this volume are given a penetrating treatment by authors outstanding in their respective fields. The contents and authors include: "The cell membrane" by Eric Ponder; "Plant cell walls" by Kurt Mühlethaler; "Ameboid movement" by Robert Allen; "Cilia and

flagella" by Don Fawcett; "Mitochondria" and "Lysosomes" by Alex Novikoff; "Chloroplasts" by S. Granick; "Golgi apparatus" by A. J. Dalton; "The ground substance" by Keith Porter; "The interphase nucleus" by Alfred Mirsky and Syozo Osawa; and "Nucleocytoplasmic interactions in unicellular organisms" by J. Brachet.

The articles are complemented by numerous photographs that, for the most part, are excellent, and the literature reviewed appears to be more or less complete through 1960. The greatest service rendered by this book is that it gathers together and integrates existing data; hence it provides the teacher with a résumé of the present status, however transitory it may be, of the biology of the cell. In this regard, I scarcely need remark that the present rate of growth of literature in cellular biology is awesome. One wonders, therefore, whether any work of this sort can possibly have the lasting value which Wilson's book enjoyed in its day. Indeed, certain portions of this series, which were published a year or two ago, are already dated.

Although *The Cell* will undoubtedly be used chiefly by teachers and students, the pretentiousness of the published product has dictated an alarmingly high price tag for volume 2 and for the entire series. Because of the largely ephemeral nature of this volume, which, as I have indicated, is inevitable in such an active field, it is my opinion that a greater service to the scientific community would have been provided by markedly reducing its cost, thereby making it readily available to those who will actually use it.

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Ecological Signpost

Growth and Regulation of Animal Populations. Lawrence B. Slobodkin. Holt, Rinehart and Winston, New York, 1961. viii + 184 pp. Illus. $5.

During its development, ecology has profited from a number of short books, characteristically written from a highly personal point of view. Among these, works by Pearl, Lotka, Gause, Elton, and Bodenheimer have had major directing influence. This volume, a member of the spate of "series" that publishers currently cherish, goes beyond its ostensible summarizing function and may well lay claim to a place in this company. Slobodkin attempts "to indicate the present state of theory relating to the number and kinds of animals and plants that are found in nature." Starting broadly, he quickly changes focus to the elements of population and then shifts logically from birth and death rates in simple organisms to progressively more complex models of population growth and interaction. Population mathematics are well presented, although the author's statement that "anything stated in mathematical form will also be said verbally," while reassuring to the student, is not (and should not be) realized. With a critical and original discussion of energy relations and community structure, the final chapters come full circle.

The personal approach is the source of the book's main strengths and weaknesses. The somewhat irreverent style is appealing, and the first chapter—on man in the ecological world—is an unsurpassed, concise presentation of this overwritten and underemployed subject. The choice of subjects to discuss and to omit has been made well. The book as a whole is marvelously cohesive. However, the neglect of much pertinent literature is regrettable, and the virtual absence of basic data is worse. A seeming plea for pedantry may be in order at a time when short, specialized books are becoming so popular. Where details of methodology become part of substance, as, in my opinion, they do here, they must not be sacrificed for lack either of space or of personal interest. Besides the usual errors that plague a first printing, there are a number of ambiguities and heterodoxies. At least some of these may be intentional, since they are provocative rather than provoking. In its function of reflecting the present state of theory, the book gives ample indication that some of the invidious divisions within ecology are beginning to be bridged. It does less well by some of the current controversies. Finally, by failing to consider them, it reveals areas of current neglect. For example, parasitism, commensalism, and mutualism do not even receive short shrift. More significant than the fidelity of the book as a mirror, however, is the fact that it manages, despite its brevity, to serve as a signpost.

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Biology and Medicine

Medizinische Grundlagenforschung. vol. 3. K. Fr. Bauer, Ed. Thieme, Stuttgart, Germany, 1960 (order from Intercontinental Medical Book, New York). 762 pp. Illus. DM. 178.

In volume 3, as in the previous volumes of this series, actual problems of medicine and its allied fields are presented by internationally known experts; their goal is to give information about the progress in certain selected disciplines and to find a synthesis of the different, apparently diverging, tendencies in modern medical-biological research.

The individual chapters (15) deal with such problems as radiation protection, exposure of human beings to radioactivity, protein research, fat metabolism and arteriosclerosis, blood coagulation, structure and function of different tissues and systems, and the present state of information and knowledge in the field of evolution, to mention a few.

The presentation in general is quite dynamic, makes interesting reading, and stimulates the development of one's own ideas. The book's format is excellent, and the volume is a valuable contribution to medicine and biology.

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A Scholar's Approach

A History of Medicine. vol. 2, *Early Greek, Hindu, and Persian Medicine*. Henry E. Sigerist. Oxford University Press, New York, 1961. 352 pp. Illus. $11.

In the foreword to volume 1 of his proposed eight-volume *History of Medicine*, the late Henry E. Sigerist provided an insight into his undertaking. He "had resolved to write a history of medicine that would approach the subject from a somewhat different angle." The methodological introduction which followed gave clear indication of the "new angles" to be explored. Medicine was viewed as having a scope much broader than the actions of the physician. Thus the historian of medicine must concern himself with the "promotion of health, the prevention of illness, the restoration of health and rehabilitation of the patient."

Many factors must be examined for

their effect on health, but none seemed more important to Sigerist than geography and economics. Recognizing that "medical theories always represent one aspect of the general civilization of a period," Sigerist concluded that "in order to understand them fully we must be familiar with the other manifestations of that civilization. . . ." The history of medicine then could be written successfully only when placed in its social and cultural context. It is this approach which marked the contributions of Sigerist to a field of history that is almost as old as the practice of medicine itself.

As originally conceived, volume 2 was to deal with Greek, Indian, and Persian medicine in their totality. But at the time of his death Sigerist had brought to completion only material dealing with the early periods. Of these the section on Persia suffers most, for ancient Persia made little contribution to the development of medicine. The scholar can regret that the study did not reach the 10th and 11th centuries of the modern era, the period during which Persian civilization flourished under the influence of Islam and in which Persian medicine reached its zenith. Surely Sigerist would have provided interesting insights into the problems surrounding the relations between society, religion, and medicine during this important period in Middle Eastern history.

The organization of the remaining sections follows the system adopted in the first volume; thus a chapter is devoted to the "setting" of ancient India and another to the early Indus civilization. The lengthy chapter, "Life in the Greek city-states," provides an excellent study of the place of medicine and hygiene in early Greek society.

Sigerist was aware of the importance of religious and philosophic trends in the development of medical thought and practice; and setting the medicine of ancient India alongside that of ancient Greece brings into sharp contrast the relatively advanced empirical and rational content of the latter as compared to the religious spirit of the former.

This volume was edited and brought through publication by Ludwig Edelstein and Miriam Drabkin; they also share responsibility for the excellent choice of illustrations.

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New Books

Mathematics, Physical Sciences, and Engineering

Chemical Thermodynamics. John G. Kirkwood and Irwin Oppenheim. McGraw-Hill, New York, 1961. 270 pp. Illus. $8.75.

Comprehensive Inorganic Chemistry. vol. 8, *Sulfur, Selenium, Tellurium, Polonium, and Oxygen.* Robert C. Brasted. Van Nostrand, Princeton, N.J., 1961. 315 pp. Illus. $10.

Creative Problems in Engineering Graphics. Ernest R. Wiedhaas. McGraw-Hill, New York, 1961. 50 pp.

Demineralization by Electrodialysis. J. R. Wilson, Ed. Butterworths, Washington, D.C., 1960. 393 pp. Illus. $14.

Fourier Transforms and Convolutions for the Experimentalist. R. C. Jennison. Pergamon, New York, 1961. 126 pp. Illus. $5.

Fundamentals of Scientific Mathematics. George E. Owen. Johns Hopkins Press, Baltimore, Md., 1961. 284 pp. Illus. $5.

Geology of the Atlantic and Gulf Coastal Province of North America. Grover E. Murray. Harper, New York, 1961. 709 pp. Illus. $24.

Graphics. John T. Rule and Steven A. Coons. McGraw-Hill, New York, 1961. 491 pp. Illus. $8.95.

Handbook of Automation, Computation, and Control. vol. 3, *Systems and Components.* Eugene M. Grabbe, Simon Ramo, and Dean E. Wooldridge, Eds. Wiley, New York, 1961. 1047 pp. Illus. $19.75.

Handbook of Numerical Methods for the Solution of Algebraic and Transcendental Equations. V. L. Zaguskin. Translated from the Russian by G. O. Harding. Pergamon, New York, 1961. 214 pp. Illus. $6.50.

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Linear Differential Operators. Cornelius Lanczos. Van Nostrand, Princeton, N.J., 1961. 580 pp. Illus. $12.75.

Metallurgy of Elements and Compound Semiconductors. Proceedings of the Metallurgical Society Conference, 29–31 August 1960. Ralph O. Grubel, Ed. Interscience, New York, 1961. 505 pp. Illus. $13.

Modern Magnetism. L. F. Bates. Cambridge Univ. Press, New York, ed. 4, 1961. 526 pp. Illus. Paper, $2.95.

New Mathematics. A unified course for secondary schools. vol. 3. K. S. Snell and J. B. Morgan. Cambridge Univ. Press, New York, 1961. 373 pp. $2.50.

Physical Mechanics. Robert Bruce Lindsay. Van Nostrand, Princeton, N.J., ed. 3, 1961. 480 pp. Illus. $9.75.

Problems in Applied Descriptive Geometry. Matthew McNeary. McGraw-Hill, New York, 1961. 6 pp. + 21 teaching units. $3.95. Units designed for use with *Applied Descriptive Geometry* by Warner and McNeary.

Reactors. vol. 2. H. R. McK. Hyder, Ed. Pergamon, New York, 1961. 575 pp. Illus. $15.

Reports on Progress in Physics. vol. 24. A. C. Stickland, Ed. Inst. of Physics and Physical Society, London, 1961. 424 pp. Illus.

Semimicro Qualitative Analysis. A nonhydrogen sulfide system. Jacob Cornog. Houghton Mifflin, Boston, Mass., 1961. 253 pp. Illus. $5.

Separation of Heavy Metals. Anil K. De. Pergamon, New York, 1961. 307 pp. Illus. $9.

Shock Tubes. J. K. Wright. Wiley, New York, 1961. 171 pp. Illus. $2.95.

Statistical Analysis and Optimization of Systems. E. L. Peterson. Wiley, New York, 1961. 201 pp. Illus. $9.75.

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Ultraviolet and Visible Absorption Spectra. Index for 1955–1959. Herbert M. Hershenson. Academic Press, New York, 1961. 148 pp. $8.

Reprints

Anthony van Leeuwenhoek and His "Little Animals." Being some account of the father of protozoology and bacteriology and his multifarious discoveries in these disciplines. Clifford Dobell. Dover, New York, 1960. 442 pp. Illus. $2.25.

Applied Elasticity. John Prescott. Dover, New York, 1961. 666 pp. Illus. $2.95.

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Cooperation and Competition among Primitive Peoples. Margaret Mead, Ed. Beacon Press, Boston, ed. 2, 1961. 553 pp. $2.95.

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An Elementary Treatise on Elliptic Functions. Arthur Cayley. Dover, New York, ed. 2, 1961. 398 pp. Illus. $2.

Fluid Mechanics for Hydraulic Engineers. Hunter Rouse. Dover, New York, 1961. 431 pp. Illus. $2.25.

Higher Geometry. An introduction to advanced methods in analytic geometry. Frederick S. Woods. Dover, New York, 1961. 433 pp. Illus. $2.

An Introduction to the Theory of Canonical Matrices. H. W. Thurbull and A. C. Aitken. Dover, New York, 1961. 213 pp. $1.55.

The Life of Pasteur. Rene Vallery-Radot. Translated from the French by Mrs. R. L. Devonshire. Dover, New York, 1960. 505 pp. $2.

Mathematical Methods for Scientists and Engineers. Lloyd P. Smith. Dover, New York, 1961. 463 pp. Illus. $2.

Reports

Ratio of Thorium-230 to Thorium-232 in Deep-Sea Sediments

Abstract. The ionium-thorium method for age determination in deep-sea sediments is critically reviewed, and its shortcomings are discussed. A method that allows an estimate of the rate of sedimentation in the superficial layer of the sediment is presented. A formula for calculating the error in age determination by the method is given for the case when the rate of sedimentation is changing and, with it, the rate of thorium-232 sedimentation.

The increasing use of the thorium-230/thorium-232 ratio for dating deep-sea sediments (*1–4*) requires a critical review of the validity of the basic assumptions involved. As pointed out by Goldberg and Koide (*2*), these assumptions are: (i) The Th^{230}/Th^{232} ratio has remained constant in the waters adjacent to the sediments during the time interval involved. (ii) The chemical species of Th^{230} and Th^{232} in seawater are the same, and these isotopes have identical distributions. (iii) The analyzed materials do not contain detrital materials of continental or volcanic origin with significant contributions of Th^{230} or Th^{232}, or both.

The last assumption is not valid in nature because it would imply that deep-sea sediments are entirely authigenic. That this cannot be true is demonstrated by several factors, such as the rather high potassium-argon ages obtained by P. M. Hurley *et al.* (*5*), indicating that the bulk of the sediment is of terrigenous origin. This difficulty was realized by Goldberg and Koide, and a preferential dissolution of the sediment was attempted in order to obtain only the Th^{232} precipitated from seawater. The use of hot concentrated hydrochloric acid may achieve a preferential solution of thorium, but it has not been proved that only the Th^{232} that was originally precipitated together with Th^{230} is dissolved by this procedure. On the other hand, a procedure involving the total dissolution of the sediment in order to obtain the Th^{232} implies the assumption that all Th^{232} in the sediment originated from seawater. This assumption will certainly give generally inaccurate results.

A comprehensive check of the validity of the method in determining geochemical concentration is made difficult, since most investigators measure only the ratios and do not determine the actual concentration of the two thorium isotopes because of the difficulties involved in determining the chemical yield. It may be possible, however, to use the available data to demonstrate that the method must be improved considerably and handled very carefully before it can yield valuable dating results.

Picciotto and Wilgain (*1*) found 3 to 11 $\times 10^{-6}$ g of Th^{232} per gram of sediment in superficial layers of sediment from the central Pacific Ocean. Miyake and Sugimura (*4*) found values of 10 to 30 $\times 10^{-6}$ g of Th^{232} per gram of sediment for samples from the western Pacific. Goldberg and Koide do not give absolute concentrations. The Th^{230} concentrations given by Picciotto (*6*) range from 2 to 60 $\times 10^{-12}$ c/g of sediment, corresponding to 1 to 30 $\times 10^{-10}$ g of Th^{230} per gram, with values ranging from 10 to 30 in the superficial layer. Miyake and Sugimura do not give values for their samples, but maximum values can be calculated from the ratios of the thorium isotopes and the concentration of Th^{232}. Thus, a maximum value of 8 $\times 10^{-10}$ g of Th^{230} per gram of sediment is obtained. It has been shown conclusively (*6, 7*) that the Th^{230} contained in the sediment is derived mainly from the uranium dissolved in seawater and that, on the average, about 1.7 $\times 10^{-9}$ g of Th^{230} is precipitated per square meter of ocean floor per year, corresponding to the total production of Th^{230} from uranium contained in seawater (3 $\times 10^{-6}$ g of uranium per liter). This value allows the rate of sedimentation of the superficial sediment layer to be estimated in grams per square meter and year. The rate is given by the following formula:

$$\text{Rate of sedimentation} = \frac{1.7 \times 10^{-9}}{Th^{230}\ \text{concentration}}$$

The smallest possible rate for the western Pacific sediment investigated by Miyake and Sugimura is 2.5 g/m² per year, corresponding to about 4 mm of sediment per 1000 years if a water content of 50 percent is assumed. Higher water content would give higher rates. This result is higher by a factor of 10 than the rate given by Miyake and Sugimura. If the values of Picciotto and Wilgain are used, the rate of sedimentation in the central Pacific would range from 0.5 to 1.7 g/m² per year, corresponding to 0.8 to 3 mm per 1000 years (assuming a water content of 50 percent).

The amount of Th^{232} that must be precipitated per year in order to give the ratios of the two thorium isotopes found in the sediment can easily be calculated from the ratio of the isotopes in the superficial layers and the amount of Th^{230} precipitated per year. The ratio of activities obtained by Miyake and Sugimura is about 4, corresponding to a Th^{230}/Th^{232} ratio (in grams) of 23 $\times 10^{-6}$. Consequently, 7.3 $\times 10^{-5}$ g of thorium must be precipitated per square meter and year, and the same amount must be added to the ocean water in order to keep the thorium concentration constant (a general geochemical assumption). A consequence of this calculation is that river water should show the same concentration of thorium as uranium, and that this thorium should reach and be mixed into the main part of the ocean water. This is not the case for uranium, which is trapped by reducing environments in basins bordering the oceans (*7*). It seems unlikely, therefore, that only a small portion, if any, of the thorium found in deep-sea sediments is derived from thorium dissolved in ocean water. The bulk of Th^{232} used for obtaining the ratio of Th^{230} to Th^{232} must be derived from minerals of terrigenous or volcanic origin. Consequently, the third assumption listed above is not valid.

Instructions for preparing reports. Begin the report with an abstract of from 45 to 55 words. The abstract should *not* repeat phrases employed in the title. It should work with the title to give the reader a summary of the results presented in the report proper.

Type manuscripts double-spaced and submit one ribbon copy and one carbon copy.

Limit the report proper to the equivalent of 1200 words. This space includes that occupied by illustrative material as well as by the references and notes.

Limit illustrative material to *one* 2-column figure (that is, a figure whose width equals two columns of text) or to *one* 2-column table or to *two* 1-column illustrations, which may consist of two figures or two tables or one of each.

For further details see "Suggestions to contributors" [*Science* **125**, 16 (1957)].

If we now assume that Th^{232} in deep-sea sediments is a constituent of the nonauthigenic minerals, the dates obtained by the use of the ratio are subjected to rather large errors, since the rate of sedimentation may change with time as Broecker, Turekian, and Heezen (*8*) have shown. The postglacial rate of noncarbonate sedimentation in the equatorial Atlantic is only one-third or less of that during the last glacial age. A smaller change can be expected in the Pacific. This change would alter the Th^{230}/Th^{232} ratio by the same factor when the rate of Th^{230} precipitation from seawater is assumed to have remained constant. It can easily be shown that the error in the age determination becomes

$$t_1 - t = \frac{1}{\lambda_{t_0} - \lambda_{th}} \ln p = 1.1 \times 10^5 \ln p \text{ years}$$

where t_1 is the age obtained under the assumption that the rate of sedimentation has not changed, t is the real age, and p is the ratio of the rates of sedimentation at the deeper level to the recent rate of sedimentation. If the rate has changed by a factor e, the error becomes as large as 110,000 years. Already a change of 38 percent causes an error of 52,000 years. This would explain the low rates of sedimentation obtained by Miyake and Sugimura.

In general, it can be concluded that the Th^{230}/Th^{232} methods will not give correct ages or rates of sedimentation unless the basic assumptions are carefully controlled and investigated. In fact, in the Caribbean cores dated by the ratio of Pa^{231} to Th^{230} (*9*), the ratio of Th^{230} to Th^{232} was shown to give conspicuously discrepant ages (*10*).

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18 July 1961

Sex as Regulator of Triglyceride Metabolism in the Mosquito

Abstract. The female mosquito, in contrast to the male mosquito or the male and female house fly, synthesizes triglycerides when maintained on glucose; after 7 days, the amount of triglycerides in the female may be 50 times that in the male. Polyunsaturated fatty acids are absent from the newly synthesized triglycerides.

Labeled precursors of metabolic products facilitate the study of biosynthesis, since newly formed products can be differentiated from products already present. In living animals, however, quantitative estimation of synthesis from labeled precursors requires a steady state, detailed knowledge of specific activity-time relationships between precursors and product, or knowledge of the distribution of the product over many metabolic pools. It is therefore customary to carry out studies of biosynthesis in vitro, where the specific activity of the environment can be kept constant, but where the physiological control mechanisms of the intact animal are no longer functional. To study synthesis of triglycerides in vivo, we have used the adult female mosquito because it can be starved until virtually no triglycerides remain. Therefore, the triglycerides that appear after subsequent feeding on a lipid-free diet are due entirely to new synthesis.

Adult mosquitoes [*Aedes sollicitans* (Walker) and *A. taeniorhynchus* (Wied.)] were obtained from larvae reared at 25°C on rabbit pellets and yeast. House flies (*Musca domestica* L., susceptible strain) were obtained as pupae from the U.S. Department of Agriculture, Orlando, Florida. Within 2 hours after emergence, males and females were selected and kept at 25°C in glass jars provided with a moist cheesecloth pad and a feeding vial containing a cheesecloth wick soaked in 10-percent glucose solution. The glass jars and the feeding solution were changed daily. Duplicate samples of ten mosquitoes or three flies each were killed at various intervals by brief exposure to chloroform vapor. This pooling of samples reduced biological variation between duplicates to 10 percent or less. The insects were homogenized, and the homogenate was extracted twice with 1 ml of methanol and chloroform (1 : 1), with centrifugation after each extraction. Chloroform (2 ml) was added, methanol and water-soluble impurities were removed by washing twice with ½ ml of water, phospholipids were absorbed by shaking the chloroform eluate with 100 mg of silicic acid, and triglycerides were determined from the glycerol moiety (*1*). Phospholipids were determined (*2*) after elution from the silicic acid with 2 ml of methanol.

On emergence, triglyceride levels of males and females were quite similar. Subsequently, triglycerides of the male and female house flies and of the male mosquito diminished gradually. By contrast, the female mosquito (both *Aedes sollicitans* and *A. taeniorhynchus*) showed a constant net synthesis of triglycerides from the first until the sixth or seventh day after emergence (Fig. 1), ranging from 70 to 115 μg/day in different experiments. At the maximum, the amount of triglycerides may exceed the lipid-free dry weight. In the same interval, the triglycerides in the male dropped to 10 to 20 μg (Fig. 1*A*). The observed differences were not due to

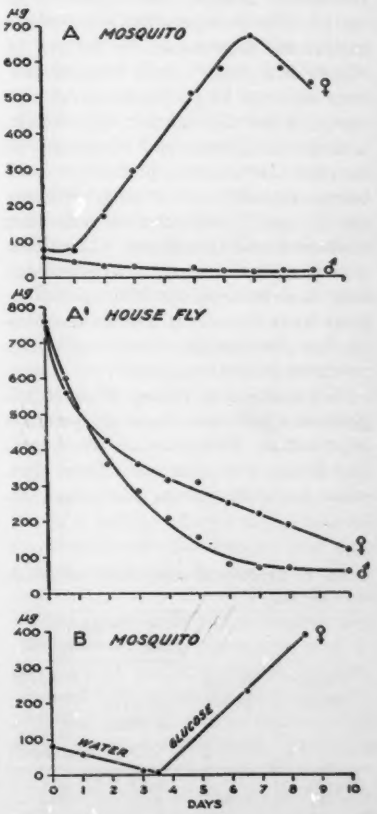

Fig. 1. Triglyceride levels of *Aedes sollicitans* (*A*) and *Musca domestica* (*A'*) maintained on glucose after emergence. (*B*) Triglyceride levels of *Aedes sollicitans* that were maintained on water and then fed glucose.

differences in food intake. Both sexes fed freely on glucose, as evidenced by distended abdomens. When maintained on water, the female catabolized 20 μg/day from emergence until death, so that additions to the pool from the different metabolic compartments and utilization by tissues take place at a constant rate.

At emergence, phospholipids and triglycerides comprised more than 90 percent of the total lipids. Free fatty acids and hydrocarbons made up the balance. Phospholipid levels remained virtually unchanged during the entire experiment (46 ± 3 μg per female, 36 ± 4 μg per male mosquito; 240 ± 20 μg per house fly). Sterols (free cholesterol, including 10 to 35 percent dehydrocholesterol) were found in amounts of only 0.1 μg per mosquito.

In order to establish the composition of the fatty acids synthesized solely from glucose, mosquitoes were maintained on water until the triglyceride level was down to 5 μg and then fed 10-percent glucose for 5 days (Fig. 1*B*). At that point, methyl esters of the triglyceride fatty acids, 99 percent of which had been newly synthesized, were subjected to gas-liquid chromatography (Table 1). Palmitic, palmitoleic, and oleic acid comprised 92 percent of the new fatty acids, palmitoleic acid being one-third of the total. Whereas the 5 μg of triglycerides left after starvation still contained 12 percent linoleic acid, this amount is represented only as a trace in the 400 μg synthesized from glucose. It is therefore likely that the mosquito does not make polyunsaturated fatty acids.

A continuously falling level of triglycerides does not necessarily preclude all synthesis. Robbins *et al.* (*3*) showed that female and male adult house flies, when fed milk powder and sugar, incorporate C^{14}-labeled acetate in the saponifiable lipid fraction, but these workers did not separate phospholipids from triglycerides.

Table 1. Triglyceride fatty acids in female mosquitoes (*5*).

Chain length	Double bonds	Amount (μg per mosquito)	
		3½ days on water	3½ days on water plus 5 days on glucose
Short (6-12)		0.02	1
14	0	0.08	12
14	1	0.01	2
16	0	1.46	140
16	1	1.20	136
18	0	0.27	14
18	1	1.36	95
18	2	0.60	Trace
Long		Trace	Trace

The ability of the female mosquito to build a huge fat body from glucose at a constant rate, as contrasted with the female house fly or the male mosquito, may facilitate the study of physiological factors that control lipogenesis in vivo (*4*).

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4. This work was supported by a grant (E-3112) from the National Institutes of Health.
5. The data in Table 1 were provided by Dr. Leon Swell, Veterans Administration Center, Martinsburg, W. Va.

10 August 1961

Licking Rates in Infant Albino Rats

Abstract. Two groups of neonatal rats raised from birth without the opportunity to drink, and tested at different age levels, exhibited the same general characteristics of licking rate that adult rats do. This suggests that licking in the rat is organized on a genetic-maturational basis.

The purpose of the experiment reported here was to determine whether constancies in licking rate reported for adult albino rats are found also in infant rats. Other workers (*1*, *2*) have reported a mean licking rate in adults of 6 to 7 licks per second and a range from 5 to a little over 8 licks per second, with the mean rate constant in both sexes for varying levels of thirst, and for water, sucrose, saccharin, and saline solutions.

In the absence of evidence to the contrary, it might be argued that these constancies are the result of reinforcement of certain rates of licking. On the other hand, if rats raised from birth without an opportunity to drink displayed, when tested at different age levels, the same licking rate as adults, it would suggest that drinking in the rat is primarily a genetically and maturationally determined response.

We tested two litters of neonatal rats from the colony maintained by the University of Missouri. Each litter was composed of 3 males and 3 females. Each litter was reared with the mother from birth until the first test day, then was separated from her and housed in a separate cage. The water supply for the mother was suspended from the ceiling of the cage, and thus the young rats were prevented from drinking prior to the first test day. Both litters had unlimited access to dry food prior to weaning and throughout all the testing and maintenance periods. The normal weaning age in the rat is between 21 and 28 days (*3*). The rats in group 1 were weaned at noon of the 21st day after birth; they were then tested daily, at 8 P.M. and 8 A.M., for 5 days. The rats in group 2 were weaned at noon of the 18th day and were tested at 4 P.M. and 8 P.M. on the first day and at 8 A.M., noon, and 8 P.M. on the four following days. All test sessions were 30 minutes long.

The apparatus consisted of six Hoeltge HB-11 cages with attached floor-mounted plastic drinking cups and 50-ml glass tube reservoirs. The mouth of the cup was 10 mm in diameter. The test solution was water. Each time the animal's tongue came in contact with the water, an electronic circuit was completed, an 8-μa current passed through its body, and a record of the tongue lap was recorded on an Esterline Angus tape moving at 1.905 cm/sec. The experimental room was maintained at a temperature between 76° and 78°F throughout the experiment.

Four licking rates were measured: The rate at the time of contact with the drinking cup; the rate in the first burst of licking of at least 1-second duration in each session; the rate within sessions; and the rate within bursts of more than 1-second duration. The means and the range of responding in the initial contact with the drinking cup and in the first burst of licking of at least 1-second duration in the first four sessions are presented in Table 1. For both groups, the mean rate of licking on first contact with the cup parallels the mean rate of licking in adult animals. Individual rates show some variability. On its initial contact with the cup in the first test session, rat F2 in group 1 licked at the rate of 9.5 licks per second. In the second test session, rats F3 and M3 in group 1 licked at the rate of 11.4 and 9.5 licks per second, respectively. Similarly, in the first test session both F1 and F3 in group 2 licked at the rate of 9.1 licks per second, and M2 licked at the rate of 9.5 licks per second. No systematic relationship between sex and licking rate was observed in either group.

Table 1. Means rate of licking, and range, on first contact with the cup and in the first burst of at least 1-second duration.

Session	Rate on initial contact (licks per second)		Rate in first 1-second burst (licks per second)	
	Mean	Range	Mean	Range
		Group 1		
1	7.3	6.3– 9.5	7.2	5.8–8.3
2	8.4	6.3–11.4	7.5	6.6–9.5
3	8.0	7.0– 9.1	7.4	6.0–8.7
4	7.7	6.9– 8.2	7.2	5.9–8.7
		Group 2		
1	8.3	6.5– 9.5	7.0	6.5–7.3
2	7.5	5.3– 9.5	6.6	5.3–7.3
3	8.1	7.1– 9.5	7.2	6.7–7.7
4	7.8	6.9– 8.6	7.8	6.9–8.6

Keehn and Arnold (*2*) have reported a decrement in mean licking rate within sessions of about 1 lick per second in adult rats. Group means for the first and last bursts of licking of at least 1-second duration in session 1 and for the first and last bursts of licking in the first 5 minutes in sessions 2 and 3 indicate that the decrement in licking rate within sessions found in adults is also found in infant rats, even in their first drinking response. For sessions 1, 2, and 3, respectively, the mean initial and terminal rates for group 1 were 7.2 and 6.1; 7.5 and 6.0; and 7.4 and 6.1. The corresponding rates for group 2 were 7.0 and 6.0; 6.6 and 6.0; and 7.2 and 6.1.

Collier (*4*), in making an analysis of rates of licking within bursts in adult rats, found (i) that the initial rate of responding is frequently as high as 9 licks per second, and (ii) that in sustained bursts of licking, high initial rates quickly decrease to a terminal rate between 6 and a little over 8 licks per second, with the mean licking rate typically falling between these values. An analysis of rates of licking within bursts of over 1-second duration in the young rats indicated that by the third session there were animals in both groups whose initial rates of responding were as high as 9.0 licks per second and whose terminal rates within the same burst were as low as 5.2 licks per second. A typical pattern of response within bursts is illustrated by one animal whose initial rate of responding in the first second was 9.0 and whose rate then dropped, over successive seconds, to 6.7, 6.0, 5.7, 5.5, and finally 5.2 licks per second, with a mean for the burst of 6.6 licks per second. Within bursts, decrements of this magnitude were found only in the beginning of the test sessions, and rates higher than 8 licks per second were never found in the middle or terminal sections of bursts sustained for more than several seconds.

The general stability of licking rates suggests that drinking in the rat is probably reflexive. Whether the licking rate is wholly determined genetically and maturationally or whether some learning is involved is a question that needs further investigation. Even when the rat is raised without an opportunity to drink, nursing and grooming may possibly produce learning effects for licking (*5*).

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14 August 1961

Complement Fixation by Antibody Fragments

Abstract. Rabbit antibodies (7*S*) degraded by papain into univalent 3.5*S* fragments fail to fix complement when they combine, but do not precipitate, with the homologous antigens. Divalent 5*S* fragments obtained by pepsin digestion (composed of fragment I linked to II, but lacking fragment III) also fail to fix complement although they precipitate with homologous antigens. The amount of specific precipitate formed by the 5*S* antibody fragment is not increased by exposure to complement.

In 1904 Ehrlich and Morgenroth proposed that antibody combines with complement by means of a specific "complementophilic" haptophore (= combining) group, distinct from the combining group for antigen (*1*). In the ensuing years evidence for the existence of a combining group for complement has not been forthcoming (*2*) and Ehrlich's theory has been largely abandoned (*2*, *3*). The present report describes experiments suggesting that group(s) essential for complement fixation exist which are distinct from the antigen-combining sites of the antibody molecule.

Rabbit antibodies against crystalline hen egg albumin, crystalline bovine plasma albumin, and type 6 pneumococcal polysaccharide, all predominantly of the 7*S* variety, were broken down to 3.5*S* fragments with papain, cysteine, and sodium ethylenediaminetetraacetate, according to the method of Porter (*4*). The reaction of these nonprecipitating preparations with the homologous antigens was studied by means of the quantitative complement fixation reaction (*5*) over a wide range of antigen concentration, extending from 1/64 to 1024 times the concentration of antigen giving maximal complement fixation with the same dilution of native antibody. No complement fixation was detected after 18 hours' incubation at 4°C either in 10 ml or 3 ml final volume. The same concentration of native antibody fixed from 20 to 40 of 50 50-percent hemolytic units of guinea pig complement. A representative experiment is illustrated in Fig. 1. Essentially similar results have been obtained by Ovary (*6*).

These experiments can be interpreted in at least two ways, which are not mutually exclusive. The first interpretation is: complement is not fixed because aggregation does not occur with the nonprecipitating, univalent antibody fragments obtained with papain digestion (*4*, *7*). The formation of a lattice of aggregating antigen-antibody complexes is widely believed to be essential for complement fixation, because antihapten antibodies do not fix complement when they combine but do not precipitate with univalent haptens (although they both precipitate and fix complement with multivalent haptens) (*8*) and because antigen excess inhibits both the formation of a lattice of aggregating antigen-antibody complexes and complement fixation (*9*).

The second interpretation is: complement fixation does not occur because the antigen combining groups of the antibody molecules have been cleaved from structure(s) essential for complement fixation. Evidence supporting this interpretation, but not contradicting the

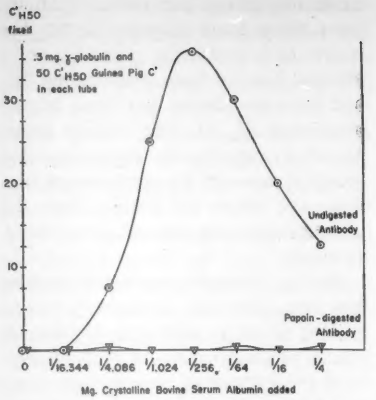

Fig. 1. Quantitative complement fixation at 4°C for 18 hours in 10 ml total volume.

first, was obtained by experiments with 5*S* antibody fragments, which are bivalent and precipitate with the homologous antigens, and comprise fragments I and II, but lack fragment III of Porter. The 5*S* fragments were prepared by means of pepsin digestion, according to the method of Nisonoff (*10*), from the rabbit antibodies previously mentioned.

Quantitative complement fixation tests done over the same wide range of antigen concentration failed to show complement fixation by the 5*S* antibody fragments. No complement fixation was detected even when the concentration of the fragment was increased 5 times over that of native antibody which was able to fix 40 of 50 50-percent hemolytic units. Addition of the chromatographically separated fragment III (*4*) from normal rabbit gamma globulin failed to restore the complement-fixing capacity of these 5*S* antibody fragments.

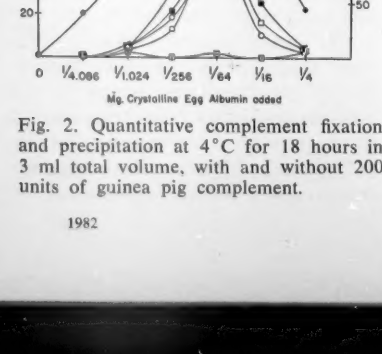

Fig. 2. Quantitative complement fixation and precipitation at 4°C for 18 hours in 3 ml total volume, with and without 200 units of guinea pig complement.

To study more closely the relationship between specific precipitation and complement fixation, the amount of the precipitates and the loss of hemolytic complement in the supernatants were determined in the same test tubes after 18 hours' incubation at 4°C (with 3 ml total volume). Large amounts of complement were used, which allowed determination of complement fixation not only by the decrease of the ability of the supernatants to lyse sensitized red cells, but also by the increase in the amount of precipitates.

A representative experiment is illustrated in Fig. 2. In the absence of complement, the amounts of precipitate obtained with 2 mg of gamma globulin of the 5*S* preparation are greater than those obtained with 1 mg of undigested gamma globulin. However, the undigested antibody fixed up to 110 of 200 50-percent units of complement, but pepsin-digested antibody fragments fixed less than detectable amounts. Moreover, complement consistently increased the specific precipitation of undigested antibody, as expected (*11*), but not the precipitation of the 5*S* fragments. The experiments thus provide two independent indications that the 5*S* fragments do not fix complement, despite specific precipitation with antigen.

It appears, therefore, that the antigen combining fragments I and II, whether separated (as in papain-digested antibody) or united (as in pepsin-digested antibody) are no longer able to fix complement. Whether this results from an alteration in the spatial arrangement of the antigen combining sites of the molecules or from the loss of certain structures in fragment III essential for complement fixation remains to be determined (*12*).

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10 July 1961

International Geophysical Calendar for 1962

Abstract. Coordination of certain types of geophysical observations and analyses throughout the world is accomplished by the advance selection of days and intervals for such work. A committee under the International Council of Scientific Unions has issued the calendar for 1962, together with a brief explanation and examples of how it may be used in planning geophysical programs.

The International Geophysical Calendar 1962 (Fig. 1) (*1*) designates selected days and intervals for special attention for geophysical experiments and analysis during 1962 and is thus a framework for world-wide coordination. It serves mainly the branches of geophysics dealing with the earth's atmosphere in which many phenomena vary significantly during the course of a year. In some experiments, such as the routine recording of variations of the earth's magnetic field, the observational and analysis programs at observatories are normally carried out at a uniform level throughout the year; in these cases the calendar is not needed. However, in many other experiments (for example, rocket experiments), it is not practical or meaningful to carry out the same program on each and every day. Here the calendar can provide a useful mechanism for coordination: experimenters will know that their colleagues in other countries, in other laboratories, and in other disciplines will tend to carry out experiments on the days or intervals marked on the calendar. In this way, results of experiments may later be more easily and usefully compared.

In some scientific fields, international scientific organizations have made specific recommendations for programs to be done on days or intervals marked on

the calendar. In others, the arrangements are informal or self-evident. Some examples are given below.

Regular World Days are intended for observations or analyses or special experiments which as a practical matter, can be carried out only about 10 percent of the time and should be spaced throughout the year. Examples in the field of ionospheric physics are oblique incidence pulse transmission and reception; absorption measurement by pulse reflection technique; extended observations of "whistlers" and very-low-frequency emissions; vertical sounding ionograms by *f*-plot, *h'*-plot, and so on; hourly reduction from ionograms of *F*-region true height parameters *hc* and *qc*.

The Regular World Days with highest priority are for similar work which can be undertaken only 1 day each month. A specific example is the program recommended by the International Scientific Radio Union (URSI) for exchange of copies of original ionograms in ionospheric vertical sounding work.

World Synoptic Intervals are intended for experiments that for practical reasons cannot be carried on continuously, but for which statistics of seasonal variations are especially needed. To simplify the calendar, the Regular World Intervals, World Meteorological Intervals, and International Rocket Weeks of past years have been combined for 1962 into one set of intervals. For the sake of the synoptic meteorological rocket programs, designated by the Committee on Space Research and the World Meteorological Organization (WMO), the intervals have been placed about a month after the equinoxes and solstices—the times of marked seasonal change in certain upper-air meteorological phenomena. During World Synoptic Intervals, meteorological rockets at a network of stations are launched at least once daily. Balloon sounding programs, either with special instruments or launchings to unusually high balloon altitudes, have been planned during these intervals. Ionospheric drift and high-atmosphere wind measurements are other examples of suitable programs for such intervals. In several disciplines, sample detailed data will provide a sampling of variations throughout the year, but with improved statistics during 1 month of each season.

Other special days marked on the calendar include the days of solar eclipses, two in 1962 and one in January 1963, when special programs may be expected to be carried out in appropriate parts of the world to study the sun and any effect of eclipses on the earth's atmosphere. Ionospheric stations customarily increase their observational programs even if the magnitude of eclipse at their location is small. Many solar-activity observatories take extra observations and issue specially detailed reports to assist in the interpretation of the geophysical effects. Also shown are days when meteor-shower activity is unusual. These include some of the important visible meteor showers and also unusual showers observable mainly by radio and radar techniques. Attention is also called to these days in case ionization produced by meteors may account for unusual effects in other geophysical experiments. The Annual World Meteorological Day, selected as 23 March (not marked on the calendar), was first celebrated in 1961. Its purpose is to make the services which national meteorological services can render to economic development, as well as the activities of the World Meteorological Organization, better known and appreciated by the people of all countries.

Special intervals not appearing on the calendar—periods of great magnetic, auroral, and ionospheric disturbance are also of considerable geophysical interest. World-wide coordination of observation is especially useful for stations not near the auroral zones, that is, places where the beginning of a major disturbance may not be immediately apparent from local observation. Notices of Geophysical Alerts and Special World Intervals are distributed by telegram or radio broadcast on a current basis by the solar-geophysical Regional Warning Centers, whose telegraph addresses are as follows: AGIWARN WASHINGTON (U.S.A.), DEMPA KOKUBUNJI (Japan), NIZMIR MOSCOW (U.S.S.R.), IONOSPHARE DARMSTADT (G.F.R.) or GENTELABO PARIS (France) or AGI NEDERHORSTDENBERG (Netherlands). The meteorological telecommunications net-

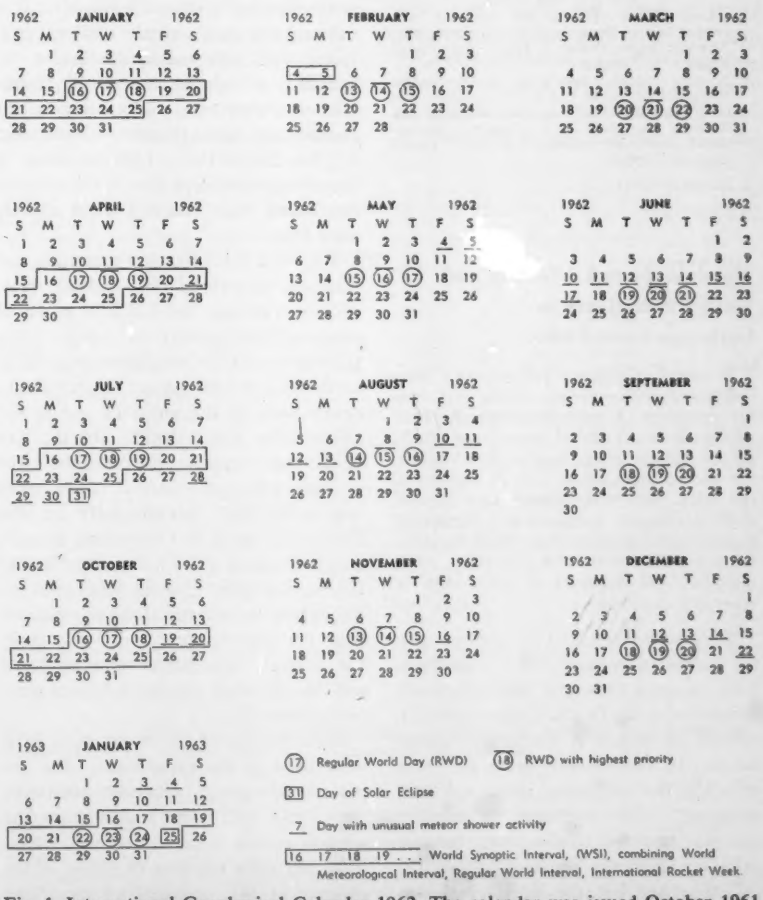

Fig. 1. International Geophysical Calendar 1962. The calendar was issued October 1961 by the International World Day Service under the auspices of the International Scientific Radio Union.

work coordinated by WMO carries such information once daily soon after 1600 U.T. Many geophysical stations increase their programs or carry on special experiments during disturbed periods. Prompt notification of immediately significant geophysical observations and of major solar flare events, which have important and sometimes long-lasting geophysical effects, are also undertaken through the Regional Warning Centers.

The International World Day Service was established in 1958 by the International Council of Scientific Unions (ICSU) and is administered by the International Scientific Radio Union, 7, Place Emile Danco, Brussels 18, Belgium. This calendar has been drawn up by A. H. Shapley and J. V. Lincoln in consultation with interested unions and committees of the ICSU and representatives of the WMO (*2*).

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1. Copies of the calendar are available upon request to the Secretary General, International Scientific Radio Union, 7, Place Emile Danco, Brussels 18, Belgium.
2. A more complete description of the calendar has appeared in the *U.R.S.I. Information Bulletin* and other widely available scientific publications. See also, A. H. Shapley, "International geophysical calendar for 1961," *Science* **132**, 1941 (1960).

2 November 1961

Vaccinia Dermal Infection and Methylcholanthrene in Cortisone-Treated Mice

Abstract. Cortisone-treated mice were inoculated with vaccinia virus, and then five paintings of methylcholanthrene were applied over the site of inoculation. In 70 percent of the mice, tumors developed at the site of inoculation, and 35 percent of the mice, with and without skin tumors, also developed lymphomas. Identically treated control mice that were vaccinia-immune developed a significantly lower incidence (38 percent) of both skin tumors and lymphomas.

F. Duran-Reynals (*1*) showed that in cortisone-treated mice inoculated with vaccinia virus into skin previously painted with methylcholanthrene (MC), tumors developed at the site of inoculation. In these experiments the mice received the following: first, ten MC paintings; next, cortisone to enhance the skin response to the virus, because mice are naturally resistant to vaccinia infection; and last, the virus, which was inoculated into the painted flank. Skin ulcers developed at the site of inoculation and healed within 3 weeks, forming a hyperplastic scar. Several weeks later tumors, frequently malignant, developed at the site of the scar in 66 percent of the mice.

Table 1. Different types of neoplasia in mice that received cortisone, vaccinia virus, and MC and in identically treated control mice that were vaccinia immune.

Neoplasia	Mice with neoplasia (No.)	
	Experimental	Control
Papilloma	5	2
Carcinoma	10*	3
Sarcoma	9†	6
Lymphoma	6	3
Total‡	30 (34)	14 (36)

* Two of this group also developed lymphomas. † Four of this group also developed lymphomas. ‡ The total number of mice included in each group is shown in parentheses.

The procedure was reversed in the present experiments. That is, cortisone-treated mice were first inoculated with the virus, and then MC was applied over the site of inoculation. Results similar to those previously reported (*1*) were obtained with much less MC. The tumors appeared much earlier, grew faster, and were mostly malignant. In addition, a high incidence of lymphomas was observed, particularly in the absence of skin tumors. Mazurenko (*2*) has shown that a high incidence of lymphomas develops late in life in mice inoculated with vaccinia virus shortly after birth.

We used the following materials and methods: noninbred albino female mice, 16 weeks of age; the Levaditi strain of neurovaccinia grown in rabbit testes (infective titer for the rabbit skin 10^{-9}); cortisone (cortone acetate) injected subcutaneously in the groin (1 mg in 0.1 saline daily for 5 days). On the day of the last cortisone injection, the virus or an extract from normal rabbit testes was inoculated intradermally in the flank (0.1 ml of a 1:10 saline suspension). Beginning 24 hours after inoculation, 1-percent 3-methylcholanthrene in benzene or benzene alone was painted over the shaved back and flanks daily for 5 days. The mice were observed until death, when routine autopsies were performed (*3*).

Nine groups of about 40 mice each were used in the experiment. The experimental group received cortisone, virus, and MC. The results from the control groups were as follows. Cortisone and virus together or alone, in the absence of MC, induced no significant changes in the mice. Cortisone and MC or MC alone, in the absence of the virus, induced an incidence of neoplasia significantly lower than in the experimental group. Essentially the same results were obtained in vaccinia-immune control mice that received cortisone and virus and, 1 month later, received more cortisone, a second virus inoculation, and MC.

To avoid repetition, only the results from the experimental and vaccinia-immune control mice will be summarized in detail. Skin ulcers developed at the site of virus inoculation in all the experimental mice. Beginning 3 weeks after treatment, in 50 percent of the mice the virus-induced lesions showed a series of changes, such as extensive, confluent hyperplasia followed by chronic ulceration, which led to the development of malignant skin tumors. In the remaining mice the virus lesions healed rapidly forming a hyperplastic scar. Skin tumors also developed at the site of the scar in 20 percent of the mice. Thus, 3 months after treatment skin tumors had developed in 70 percent of the experimental mice and in only 16 percent of the control mice. When the experiment was terminated, neoplasia—skin tumors and lymphomas—had developed in 88 percent of the experimental mice and in 38 percent of the control mice.

The number of mice with different types of neoplasia is shown in Table 1. The number of mice with carcinomas and lymphomas appears to be significantly lower in the control group. Lymphomas developed in 25 percent of the 24 experimental mice with skin tumors and in none of the 11 control mice with skin tumors. The small size of the control group may account for this difference. In the case of mice without skin tumors, however, the size of the experimental and control groups was approximately reversed, and lymphomas developed in 60 percent of the smaller group of ten experimental mice and in only 12 percent of 25 control mice. These results have been shown to be consistently reproducible.

The results suggest that the chance of malignancy may be significantly increased in a host exposed to MC during vaccinia infection. The role that nonspecific factors, such as the skin injury and tissue repair, may play in these results is being investigated (*4*).

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4. This work was supported by grants from the National Institutes of Health and from the American Cancer Society.

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10 July 1961

Common Human Viruses as Carcinogen Vectors

Abstract. Single doses of pairs of viruses and organic carcinogens (in amounts too small in themselves to induce tumors) were administered to male Swiss mice free of polyoma virus. Malignant tumors developed in groups of mice injected with five of the carcinogen-virus pairs. Prior immunization against the virus of a pair prevented tumor formation by that pair. Carcinogen binding by poliovirus 2 was demonstrated in vitro.

It has been a continuing paradox in the field of experimental neoplasia that carcinogens strongly implicated in human tumorigenesis, though present in the human environment in only trace amounts, will ordinarily induce neoplasia in animals only when administered in relatively large amounts, or when given together with various physical or chemical "cocarcinogens" (*1*). Speculation on possible natural cocarcinogens led us to consider the role of common, nontumor viruses. Viruses are ubiquitous, often occur in family or household patterns, are most easily spread in urban environments, and with relative ease penetrate susceptible, nonimmune cells, and commonly, cell nuclei. This report (*2*) presents evidence of in vitro and in vivo interactions between common human viruses and chemical carcinogens; the results suggest a hypothesis that viruses may serve as natural vectors for the transport of otherwise innocuous amounts of environmental carcinogens (mutagens) to susceptible intranuclear chromosomal loci.

Studies were performed in vivo on male Swiss white mice (Webster strain), which were obtained from a colony proved free of polyoma virus (*3*) and which were reported to have a low incidence of *de novo* tumors (thymoma and lymphoblastic leukemia) (*4*). The viruses used (vaccinia, ECHO 9, Coxsackie B_4, and poliovirus 2) were harvested fluids of fully infected tissue cultures of monkey kidney; by the routes given, they evoked negligible mortality or morbidity. The carcinogens injected and their respective doses, judged to be too small to induce tumors (*1*), were: 9,10-dimethylbenzanthracene-1,2 (DMBA), 100 μg; 2-aminofluorene (AF), 100 μg; and 1,2,5,6-dibenzanthracene (DBA), 75 μg.

Each animal received a single dose, at the same time and in the same site, of two substances: (i) virus suspension, or frozen-thawed monkey kidney tissue culture cells, or tissue culture nutrient medium; and (ii) carcinogen or carcinogen solvent (acetone or propylene glycol). Randomized groups of 6 to 12 animals, 20 to 23 days old, were injected subcutaneously, intraperitoneally, or intranasally and dispersed in multiple cages; animals that survived for 12 months were killed. Cannibalism prior to 3 months of age was heavy, presumably because of overcrowded cages.

Lymphomas, myeloid leukemias, a reticulum cell sarcoma, and a subcutaneous fibrosarcoma—malignant tumors other than those reported to arise *de vovo* in this strain (*4*)—occurred in five groups of mice that received carcinogen-virus pairs, and in no other groups (Tables 1 and 2). The calculated probabilities (*5*) that the tumor incidences in these groups could have occurred by chance are: DMBA and vaccinia, 2.0 percent; DMBA and poliovirus 2, 0.7 percent; DMBA and Coxsackie B_4, 62 percent; AF and Coxsackie B_4, 16.5 percent; and AF and ECHO 9, 20 percent. When the chi-square test with Yates's correction is applied to all the data (Table 1), the probability that tumor incidence associated with the following conditions is due to chance alone is: virus, with and without carcinogen, $.05 > p > .01$; carcinogen, with and without virus, $.05 > p > .01$; virus plus carcinogen, $p < .01$. Four localized thymomas were found in the 161 mice alive after 3 months. Multiple pulmonary adenomas occurred in five mice that received DMBA intranasally, with or without virus.

Half of a group of 108 mice were immunized against vaccinia virus and half against frozen-thawed monkey kidney cells. Each was given a single simultaneous intraperitoneal or subcutaneous injection, as described above, of either vaccinia virus or frozen-thawed monkey kidney cells plus either DMBA or propylene glycol. The cages were not

Table 1. Results obtained by injecting mice with carcinogen-virus pairs. Data from two experiments are included.

Mice injected with carcinogen									Mice injected with carcinogen solvent		
DMBA*			AF			DBA					
No. with malignant tumors	No. alive at 3 mo.	No. injected	No. with malignant tumors	No. alive at 3 mo.	No. injected	No. with malignant tumors	No. alive at 3 mo.	No. injected	No. with malignant tumors	No. alive at 3 mo.	No. injected
With vaccinia virus											
5	9	16	0	11	16				0	8	12
With ECHO 9 virus											
0	11	22	2	7	12	0†	6	10	0	12	23
With Coxsackie B_4 virus											
1†	13	22	2	6	12	0	4	10	0	14	23
With poliovirus 2											
5	7	12				0†	6	12	0†	6	11
With tissue culture cells											
0	8	13	0	8	12				0	7	12
With tissue culture media											
0	6	10				0	6	10	0	6	10

* Pulmonary adenomas in DMBA groups: ECHO 9, 1; polio 2, 2; tissue culture cells, 1; tissue culture media, 1. † One thymoma.

Table 2. Routes, tumors, and latent periods after injection of various carcinogen-virus pairs in mice. Abbreviations: i.p., intraperitoneal; s.c., subcutaneous; i.n. intranasal.

Carcinogen-virus pair	Route	Tumor	No. of mice with tumors	Latent period (days)
DMBA and vaccinia	i.p.	Lymphoma	3	152; 239; 344
DMBA and vaccinia	i.p.	Myeloid leukemia	1	202
DMBA and vaccinia	s.c.	Fibrosarcoma	1	168
DMBA and polio 2	i.n.	Lymphoma	4	249; 307; 307; 307
DMBA and polio 2	i.n.	Myeloid leukemia	1	241
DMBA and Coxsackie B_4	i.p.	Reticulum cell sarcoma	1	307
AF and Coxsackie B_4	i.p.	Lymphoma	2	151; 202
AF and ECHO 9	i.p.	Lymphoma	2	298; 298

overcrowded. After 8 months, the only tumors observed have been four lymphomas in a group of eight mice that were not immune to vaccinia virus and were given vaccinia and DMBA intraperitoneally. The probability that this incidence could have occurred by chance—in view of a group of nine immune mice that were similarly injected and had no tumors—is 2.9 percent.

Purified suspensions of poliovirus 2 ($10^{8.9}$ to $10^{9.9}$ monkey kidney $TCID_{50}$) and vaccinia ($10^{6.8}$ $TCID_{50}$) and of their respective nucleic acids were prepared (*6*), incubated at 37°C with solutions in acetone of DMBA-9-C^{14} (*7*) containing 2.7×10^{-5} to 5.4×10^{-2} millimicromole of DMBA per milliliter, and ultracentrifuged. Measurements were made with a gas-flow counter with a sensitivity of 431 to 437 counts per minute per millimicrocurie and a background of 26 to 27 counts per minute; a precision of 0.9 to 1.5 perecent was obtained with prolonged counting times. Binding of DMBA by whole poliovirus 2 significantly in excess of that by similarly purified suspensions of frozen-thawed monkey kidney cells was demonstrated. Three separate measurements of uptake, in molecules per $TCID_{50}$, were: $17{,}000 \pm 5000$ ($p < .01$); $20{,}000 \pm 12{,}000$ ($.05 > p > .01$); and 3100 ± 900 ($p < .01$). Significant binding of DMBA by vaccinia or by virus nucleic acids was not demonstrated.

The results obtained affirm in vivo interactions of viruses and carcinogens first described by Rous and Friedewald (*8*) and by F. Duran-Reynals (*9*) and since described further by M. L. Duran-Reynals (*10*). The results are also consistent with the report by Wisely *et al.* (*11*) of enhanced chemical carcinogenesis in mice repeatedly exposed to respiratory viruses.

Although the results suggest that common viruses may serve as carcinogen vectors, other interpretations of these interactions can be made. If such interactions occur in nature, it may prove possible to reduce neoplasia currently ascribed to chemical carcinogens by immunization against a virus (*12*).

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19 June 1961

Estradiol Stimulation of Glycine Incorporation by Human Endometrium in Tissue Culture

Abstract. The incorporation of C^{14}-labeled glycine into human endometrium grown in tissue culture is accelerated by the addition of estradiol-17β to the culture medium under certain experimental conditions. This effect is accompanied by an increased rate of disappearance of the glycine from the medium, and its demonstration is dependent upon the age of the culture and the frequency with which the medium is renewed.

Estrogens appear to influence the metabolism and chemical composition of "target organs" by increasing the rates of endergonic synthetic reactions. An enzyme system which is dependent upon minute amounts of estrogens has been isolated from several of these target organs. When activated by estrogen, it catalyzes the transfer of hydrogen from reduced triphosphopyridine nucleotide to diphosphopyridine nucleotide, which may result in increased energy to accelerate the synthetic activities of the cell (*1*).

Tissue culture techniques seemed to offer a useful system for further investigations of estrogen action. Human endometrium, which shows striking morphologic responses to estrogens, can be propagated in vitro in a variety of media (*2*, *3*). Estradiol, when added to slices of endometrium in vitro, increases the rates of oxygen consumption and conversion of glucose and pyruvate to carbon dioxide. Human endometrium from different phases of the ovulatory cycle shows two peaks of oxygen consumption in vitro. These two peaks, at 6 to 10 and 22 to 24 days, correlate well with the known peak of concentration of endogenous estrogens in blood (*4*). Treatment of castrated rats with estradiol increases the subsequent rate of incorporation of radioactive glycine and formate into the protein, lipid, adenine, and guanine of surviving uteri (*5*). The estradiol-sensitive enzyme system has been identified in human endometrium (*6*). This paper is a preliminary report of the effects of estradiol on human endometrium in tissue culture.

The methods and media used were those devised by Peebles (*7*). Sterile specimens of endometrium were obtained by curettage, and sterile technique was used in all subsequent procedures. The tissue was washed once with Hanks' salt solution, then 20 ml of 0.1-percent trypsin solution was added to each specimen and the mixture was stirred rapidly for 15 minutes. The supernatant fluid was saved, and the remaining tissue fragments were treated twice more in a similar manner. The combined supernatant fluids were centrifuged at 600 rev/min for 10 minutes at 12°C. The sediment was resuspended in sufficient medium to give a final concentration of about 750,000 cells per milliliter. Each tube received 1 ml of this suspension and was incubated in a horizontal position without agitation at 35°C for the desired length of time.

The medium was composed of 5.5 parts of medium 199, 1.5 parts of beef embryo extract, 3 parts of calf serum, plus penicillin and streptomycin. Glycine-2-C^{14} and estradiol-17β were added to give final concentrations of $6.6 \times 10^{-7}M$ and $5 \times 10^{-6}M$, respectively. At the end of the growth period the medium was poured off, leaving the cells adherent to the tube wall. An equal volume of 10-percent metaphosphoric acid was added to each specimen of medium. The resulting precipitate was removed by centrifugation, and 0.1 ml of the supernatant fluid was pipetted onto stainless steel planchets, dried under an infrared light, and

Table 1. Effect of estradiol on incorporation of glycine into endometrium in tissue culture. The number of determinations made is shown in parentheses. Each sample was counted long enough to obtain a probable error of counting of less than 1 percent.

Growth	Cellular radioactivity per tube (count/min)	
	Control	Estradiol
1+	1.20 (10)	1.10 (4)
2+	1.00 (5)	
3+	1.80 (3)	2.61 (8)
4+	2.95 (2)	3.86 (5)

counted in a continuous gas flow windowless counter. The cells adhering to the tube walls were washed once with 0.9-percent sodium chloride and were then mixed with 10-percent metaphosphoric acid. The precipitate was centrifuged and transferred quantitatively, with the aid of a little water, to planchets and then dried and counted.

Attempts were made to culture nine specimens of endometrium. Four samples showed no evidence of viability after 5 days culture in the basic medium. One of these was from a postmenopausal woman, and the other three were obtained from premenopausal women shortly before their predicted menstrual periods. Of the five samples that did grow, all showed evidence of growth within 2 days. One of these was obtained 2 days after cessation of menstruation and 1 day after injection with a large dose of synthetic estrogen. Another specimen was from a patient with hyperplastic endometrium, and the other three were from women in the first 2 weeks of their ovulatory cycle. That tissue from the proliferative phase grows better than specimens from the secretory phase has been noted by other investigators (*3*).

The cultures, examined microscopically in the living state, exhibited great differences in the number of viable cells adherent to the walls of the tubes. Two basic cell types were often noted in the same tube (*3*). The greater number of cells had a long, spindle-shape, with processes which appeared to connect with other similar cells. Less often, scattered clumps of round or polygonal-shaped cells were seen.

In one incubation experiment, 43 tubes were initially planted. In addition to the basic medium, all tubes contained labeled glycine during the initial growth period; estradiol was added to 21 tubes. At the end of 3 days, there were all degrees of growth in both groups. The average amount of radioactivity per tube in the cellular material and in the medium was not significantly different in the two groups.

In another experiment three conditions were compared. The control set contained no added estradiol and the other two sets contained estradiol at concentrations of 10^{-7} and $10^{-6}M$. Each group of tubes was grown for 1 week in its own medium; then the old medium was replaced by fresh medium of the same type, and the tubes were left to grow for another week. At the end of this time, 8 of the 13 tubes containing the higher estradiol concentration showed complete cellular necrosis. All of the other tubes contained viable cultures. This prolonged exposure to estradiol appeared to bring about an early death of the cell cultures, but did not increase incorporation or utilization of glycine from the medium.

In a third experiment 40 tubes, grown in the basic medium for 3 days until growth was established, received fresh medium containing labeled glycine. Estradiol was added to half of the tubes at random, and the cultures were incubated for four more days. The degree of growth in each tube was judged by inspection and graded 1+ to 4+ (Table 1). The amount of glycine incorporated is correlated with the estimate of cellular growth, and in the two groups with greatest growth the estradiol significantly increased the incorporation. The mean for all tubes containing estradiol was 2.5 counts per minute while that for the control was 1.4 counts per minute. This difference is small, but it is statistically significant at the 1-percent confidence level (t test). The average radioactivity remaining in the medium in all of the tubes containing estradiol was 9.8 counts per minute, while the control value was 15.9 counts per minute. This difference is statistically significant at the 0.1-percent confidence level.

This experiment indicates that estradiol can increase the uptake of glycine from the medium and its incorporation into the cellular material of human endometrium in tissue culture. This effect is dependent upon the duration of contact between the tissue and medium, as shown by the second experiment. The results suggest that the method of tissue culture will be of value for future investigations into the mechanism of action of estrogens (*8*).

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8. These investigations were supported by a grant from the National Institutes of Health and by Harvard Medical School student summer research fellowship grants to one of us (G.L.R.). We are indebted to Claire E. Austin for valuable technical assistance.

31 August 1961

Action of Vasopressin on the Permeability of Mesentery

Abstract. Contemporaneous movements of Rb^{86} cations and of P^{32} orthophosphate across isolated rabbit mesentery display kinetic patterns that are generally associated with passive diffusion. Vasopressin at a concentration of 100 milliunit/ml produced a significant increase in the permeability constant for P^{32} and at the same time a significant decrease in the permeability to Rb^{86}. At lower hormone concentrations (0.1 milliunit/ml) the P^{32} response was less marked but still significant ($P < .01$), while the Rb^{86} effect was not ($P > .05$). Hyaluronidase did not mimic these actions of vasopressin.

The scientific literature is replete with studies on the actions of vasopressin (ADH) on transport systems. Ussing and Zerahn (*1*) demonstrated its stimulatory effect on the active sodium transport in frog skin and presented evidence for a similar action on the passive sodium flux. With the isolated urinary bladder of the toad (*Bufo marinus*) Leaf and Dempsey (*2*) showed that vasopressin increased active sodium transport, but they were unable to establish an effect on the passive flux. Sawyer (*3*) and others have explored the ability of this hormone to promote

Table 1. Effect of vasopressin (ADH) on the permeability of mesentery to Rb^{86} and P^{32} at 38°C.*

ADH (milliunit/ml)	Change in K (percent of control)	
	P^{32}†	Rb^{86}‡
100	+132	−33
	+ 93	−24
	+ 46	−19
10	+113	−13
	+ 52	− 9
	+ 41	− 4
1	+ 29	− 7
	+ 68	− 6
	+ 36	0
0.1	+ 32	
	+ 27	
	+ 5	

* Each pair of values represents the mesentery of a different rabbit. † Every value for P^{32} except the last is significantly different from zero at the .01 level. ‡ The first three Rb^{86} values represent changes significant at the .01 level. Other Rb^{86} values are not significant ($P > .05$).

osmotic water transfer across the bullfrog bladder wall, an action that proved to be independent of the effect of vasopressin on active sodium transport. In the mammalian kidney it has been postulated that vasopressin enhances urine concentration by making the collecting ducts more permeable to water and so favoring the passive reabsorption of water into the hyperosmotic interstitial fluid (*4*).

The isolated rabbit mesentery lends itself well to an investigation of passive ion fluxes (*5*). This tissue is a symmetrical membrane consisting of two indistinguishable layers of mesothelium separated by a layer of loose areolar connective tissue. Because of its symmetry in terms both of structure and embryogenesis, no transmesenteric electical potential is believed to exist under the conditions of these experiments. When the tissue is mounted in a simple diffusion cell without hydrostatic or osmotic gradients, the ions Rb^{86} and P^{32} orthophosphate migrate independently across the mesentery with a kinetic pattern that is generally associated with passive diffusion (*6*). The equation that describes the transfer of each isotope is

$$dQ/dt = KA(C_1 - C_2)$$

where dQ/dt represents the instantaneous ion flux, $C_1 - C_2$ the difference in tracer concentration across the membrane, A the area of the membrane, and K its permeability coefficient. Values of the latter (*6*) are proportional to the slopes of straight lines like those in Fig. 1. One surface of the mounted mesentery was superfused with a solution containing tracer amounts of the two isotopes (source solution) and an appropriate concentration of vasopressin. The other surface was bathed with a solution of identical composition, except that initially it contained no isotope or hormone (sink solution). Since isotopes and hormone concentrations in the source solution were held constant, ion transfer was indicated only by the rising radioactivity of the sink solution. Relevant technical details, including procedures for determining the activities of the individual isotopes in the mixture, have been described elsewhere (*6*). In all experiments Krebs-Ringer bicarbonate ($pH = 7.4$) was used as the base solution to which were added radioisotopes and, when appropriate, vasopressin (*7*).

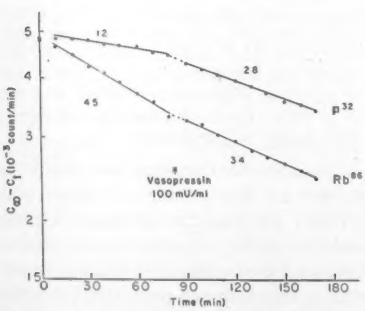

Fig. 1. The effect of vasopressin (ADH) on the contemporaneous Rb^{86} and P^{32} fluxes at 38°C. The concentration difference across the membrane ($C_2 - C_1$) is plotted on a logarithmic scale. At the time indicated by the arrow, ADH (100 milliunit/ml) was added to the source solution and maintained thereafter. The numbers above the P^{32} lines and below the Rb^{86} lines are the calculated permeability coefficients K (cm $min^{-1} \times 10^3$).

As can be seen in Fig. 1, the addition of vasopressin (100 milliunit/ml) after a suitable control period caused a prompt and sustained effect. Specifically, the anion flux increased while the cation flux decreased. In Table 1 several such experiments are summarized. With lower concentrations of the hormone both the Rb^{86} and P^{32} responses were less marked. With one exception all of the changes in K for P^{32} proved to be statistically significant. The Rb^{86} effect lost significance at a vasopressin concentration of 10 milliunit/ml, although the tendency for a decrease in the K value was still present. These permeability responses to vasopressin constitute what appears to be a unique pattern. Of more than a dozen neurohormones, drugs, and metabolic inhibitors tested in this system (*6*), vasopressin is the only substance that has caused a reduction in the Rb^{86} permeability coefficient.

Ginetzinsky (*8*) and Dicker and Eggleston (*9*) have proposed that the antidiuretic hormone acts in the kidney by releasing hyaluronidase which increases renal tubular permeability to water. When tested on rabbit mesentery in concentrations of 10 and 100 VRU/ml, hyaluronidase did not mimic vasopressin but made the membrane more permeable to both ions. It seems certain that the action of vasopressin on the permeability of isolated mesentery is not mediated through activation of endogenous hyaluronidase. Leaf (*2*), working with the toad urinary bladder, also failed to show any similarity between the actions of vasopressin and hyaluronidase.

It has been suggested that the effect of vasopressin in promoting passive water reabsorption in the mammalian kidney may be due to the opening of pores. Since the migration of Rb^{86} and P^{32} across rabbit mesentery appears to be a passive process, one might predict that the number or size of channels available for diffusion would be increased by vasopressin. However, its ability to discriminate between these two tracers is impossible to explain solely by an alteration of pore geometry. The action of vasopressin on the water flux across mesentery has not yet been established. Effects on water transport may or may not prove to be consistent with a pore hypothesis (*10*).

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3 July 1961

Hydra

Workers from many fields consider the physiology and ultrastructure of hydra and other coelenterates.

Howard M. Lenhoff

During the last decade there has been a renewed and growing interest in the use of hydra as a laboratory animal. This trend was stimulated by the contributions of W. F. Loomis, who devised methods for growing hydra in the laboratory under controlled conditions, introduced new quantitative techniques for the study of these animals, and discovered many fundamental biological phenomena, including the role of the partial pressure of carbon dioxide (pCO_2) in controlling sexual differentiation of hydra.

Since Loomis's initial discoveries, an increasing number of young workers have begun to use hydra and some other coelenterates for their experiments. These investigators represent a wide number of biological disciplines and normally do not all read or publish in the same journals. Consequently, about a year ago plans were made to acquaint these different workers with each other at a meeting having the following aims: (i) to evaluate both recent and previous work; (ii) to define current problems in the field; and (iii) most important, to effect an interdisciplinary synthesis which might otherwise take years through normal channels.

From 29 March through 2 April 1961, about 35 North American workers met for a symposium on "The Physiology and Ultrastructure of Hydra and of Some Other Coelenterates" at the Fairchild Tropical Gardens, Coral Gables, Florida. Of the five days of the symposium, only two and a half were devoted to formal sessions; the rest of the time was left open for informal discussion and expeditions to the nearby coral reefs and Everglades National Park.

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During the first session attention was focused on the ultrastructure of hydra cells, on intercellular attachments, on mesoglea, and on the nervous system. Toward the end of the session the existence of nerve cells in hydra was disputed; the light microscopists claimed that hydra has a nerve net, demonstrable by staining techniques, whereas electron microscopists were unable to find any structures resembling neural elements. The latter suggested that the interdigitations found connecting epitheliomuscular cells might serve in transmiting excitations. They also gave examples of artifacts that might be interpreted as nerve cells.

Research on the nematocyst, a structure which continues to intrigue biologists, has enjoyed a burst of activity in the last few years. The initial paper in a session on nematocysts concerned an electron-microscopic study of the origin and development of nematocysts within clusters of cnidoblasts connected by intercellular bridges. An account of the fine structure of the mature nematocyst stimulated a discussion of the mechanism of its discharge (Fig. 1).

Both the chemists and the electron microscopists presented evidence that the nematocyst capsule contained an unusual type of collagen. The nematocyst toxin was shown to be a small protein inhibiting electron transfer at the reduction of cytochrome *c*. The functions of the varied pharmacological compounds found in coelenterates, such as tetramine and serotonin, were discussed in relation to coelenterate toxins. A comprehensive evaluation of the present state of nematocyst research from the viewpoint of coelenterate systematics, natural history, and behavior concluded this session.

In a session devoted to nutrition, the first topic was the activation of the feeding reflex by reduced glutathione. Next there was a discussion of the complex nutritional requirements of hydra. New vistas to the study of both the biology and the nutrition of coelenterates were opened by a report presenting, for the first time, methods for growing separate clones of coelenterate cells (sea anemone) in tissue culture. The session ended with a stimulating discussion of the role of symbiotic intracellular algae in two unique nutritional relationships: the survival of green hydra and the calcification process by reef corals.

Attention turned in the last two sessions to problems of development and aging. Colonial hydroids were shown to be excellent experimental animals for the study of such developmental problems as (i) the manner in which an organism acquires and regulates its shape, pattern, and proportion; (ii) regression and reconstitution phenomena; (iii) physiological interactions during budding processes; and (iv) aging. The discussion on aging was highlighted by the demonstration of increased numbers of lysosomes and increased acid phosphatase activity in the aging portions of both mortal and immortal coelenterate types. Also, there was much excitement about the demonstration that even after x-irradiation of 100,000 roentgens, *Campanularia* hydranths continued to differentiate for one week.

Two papers on sexual differentiation threw new light on this complex developmental problem. The first paper emphasized a shift from chemical studies of the ambient macroenvironment to consideration of the chemistry of the microenvironment immediately

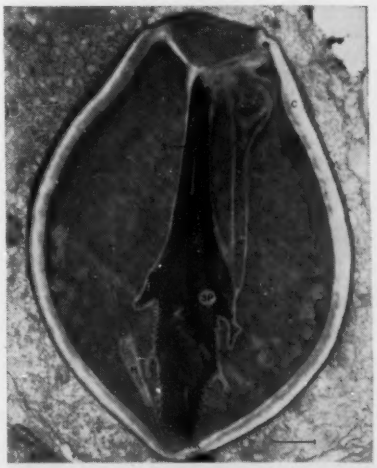


Fig. 1. Electron micrograph of a sagittal ultrathin section of a mature stenotele of hydra. *O*, Operculum; *C*, capsule; *S*, stylets; *SP*, spines; *H*, enlarged head of the internal tubule; *HK*, hook of the tubule (about × 6800). [G. B. Chapman]

surrounding each animal. This delicate interplay between the organism, microenvironment, and macroenvironment was also shown to affect differentiation in other organisms. The second paper reported apparent rhythmicities of sexual differentiation and stressed the possible role of intrinsic as well as extrinsic factors in controlling these developmental phenomena.

During the last day of the symposium papers were presented on regeneration and budding. It seemed especially fitting that such papers should be given because hydra were the first animals in which these two processes were studied. The symposium reports emphasized a chemical approach to these problems. One line of attack involved study of the effects of chemical agents on regeneration. Interestingly, it was proposed that the vitamin lipoic acid exerts its inhibitory effects on regeneration by inhibiting DPN-malic dehydrogenase. Next, the control of regeneration, growth, and cell migration were discussed in relation to postulated growth-stimulating and growth-inhibiting factors. Finally, the finding of a high DNA to protein ratio in buds as compared to the parent hydra was discussed in relation to cell growth.

One of the most refreshing aspects of this meeting was the *espirit de corps* generated among all those who took part. The participants were as follows: P. Broberg, R. Bryden, A. Burnett, G. Chapman, D. Claybrook, S. Crowell, R. Eakin, D. Fawcett, C. Fulton, G. Gauthier, T. Goreau, C. Hand, A. Hess, E. Kline, C. Lane, H. Lenhoff, Y. Li, W. Loomis, P. Lunger, C. Lytle, G. Mackie, E. Martin, L. Muscatine, E. Palincsar, H. Park, L. Passano, J. Phillips, D. Ross, D. Slautterback, D. Spangenberg, B. Strehler, S. Wainwright, E. Wangersky, J. Welsh, and R. Wood.

The proceedings and discussions of the symposium are being published by the University of Miami Press.

Forthcoming Events

December

26–31. American Assoc. for the Advancement of Science, annual, Denver, Colo. (R. L. Taylor, AAAS, 1515 Massachusetts Ave., NW, Washington 5)

The following 45 meetings are being held in conjunction with the AAAS annual meeting.

AAAS Cooperative Committee on the Teaching of Science and Mathematics (J. R. Mayor, AAAS, 1515 Massachusetts Ave., NW, Washington, D.C.). 27 Dec.

AAAS Southwestern and Rocky Mountain Div. (M. G. Anderson, New Mexico State Univ., University Park). 26–30 Dec.

Academy Conf. (J. G. Arnold, Jr., Loyola Univ., New Orleans, La.). 27–28 Dec.

Alpha Epsilon Delta (N. F. Witt, Univ. of Colorado, Boulder). 28–29 Dec.

American Astronautical Soc. (M. Pitkin, Martin-Denver Co., Denver, Colo.). 28–29 Dec.

American Astronomical Soc. (H. J. Smith, Yale Observatory, 135 Prospect St., New Haven, Conn.). 26–30 Dec.

American Economic Assoc. (K. E. Boulding, Univ. of Michigan, Ann Arbor). 26 Dec.

American Educational Research Assoc. (D. D. Feder, San Francisco State College, San Francisco, Calif.). 30 Dec.

American Nature Study Soc. (S. G. Baldwin, Danville, Ill.). 27–30 Dec.

American Physiological Soc. (R. E. Smith, Univ. of California, Los Angeles). 29 Dec.

American Political Science Assoc. (J. Korbel, Social Science Foundation, Univ. of Denver, Denver, Colo.). 27 Dec.

American Psychiatric Assoc. (D. A. Hamburg, Stanford Medical Center, Palo Alto, Calif.). 27 Dec.

American Soc. of Criminology (G. H. Barker, Dept. of Sociology, Univ. of Colorado, Boulder). 29–30 Dec.

American Soc. of Naturalists (E. W. Caspari, Univ. of Rochester, Rochester, N.Y.). 27 Dec.

American Soc. of Zoologists (R. L. Watterson, Univ. of Illinois, Urbana). 27–30 Dec.

American Sociological Assoc. (C. Taeuber, Bureau of the Census, Washington, D.C.) 29 Dec.

American Statistical Assoc. (J. A. Niederjohn, Ideal Cement Co., Denver, Colo.). 29–30 Dec.

Association of American Geographers (M. J. Loeffler, Univ. of Colorado, Denver). 26–28 Dec.

Association for Computing Machinery (W. F. Cahill, Goddard Space Flight Center, Greenbelt, Md.). 28 Dec.

Beta Beta Beta Biological Soc. (Mrs. F. G. Brooks, Box 515 Ansonia Station, New York 23). 26–27 Dec.

BIO (Biomedical Information-Processing Organization) (R. S. Ledley, Natl. Biomedical Research Foundation, Silver Spring, Md.). 27 Dec.

Biometric Society, WNAR (F. Graybill, Statistical Laboratory, Colorado State Univ., Fort Collins). 28 Dec.

Committee on Desert and Arid Zones Research, Southwestern and Rocky Mountain Div. of AAAS (T. L. Smiley, Univ. of Arizona, Tucson). 30 Dec.

Conference on Scientific Communication (C. D. Leake, Ohio State Univ., Columbus). 30 Dec.

Conference on Scientific Manpower (T. J. Mills, Natl. Science Foundation, Washington, D.C.). 27 Dec.

Ecological Soc. of America (R. S. Miller, Univ. of Saskatchewan, Saskatoon, Canada). 27–29 Dec.

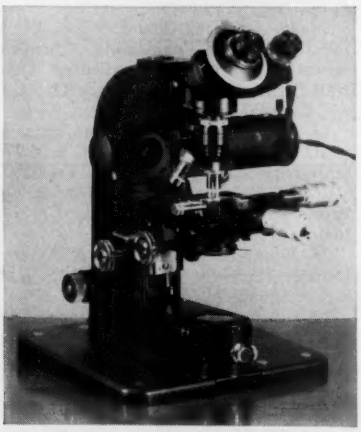
Institute of Management Sciences (M. M. Flood, Mental Health Research Inst., Univ. of Michigan, Ann Arbor). 29 Dec.

COOKE BRIEFS

Instruments and Applications

Precise traversing and measurement with the microscope

The M4005 microscope was originally designed to meet the needs of nuclear physicists who are concerned with the microscopy of charged particles in photographic emulsions. However, this instrument's facilities for precise positioning and measurement of the object are of special advantage also in the general fields of planimetry and high-power microspectrophotometry.



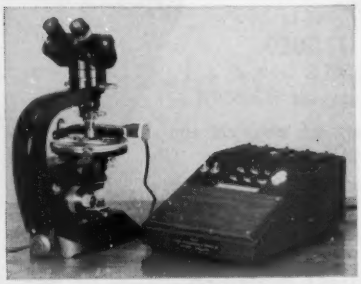
Fitted to a "universal" stand suited for use in all techniques of microscopy is a special ball-bearing stage, the top plate of which moves in either x or y axes with a "noise", or chatter, of less than 0.2 microns. Micrometers actuate the motions and these can be read to one micron.

This M4005 stand possesses a truly linear fine motion of unique accuracy which will measure depth in increments of less than one micron, this accuracy of reading being maintained throughout the whole range of its motion.

A speed procedure for area analyses and particle counts

In these routine quantitative procedures involving the microscope, speed and efficiency are major factors. Operator fatigue in this exacting work is an important consideration. It can result on the one hand in substantial inaccuracies or, if allowed for in planning the tests (with expense here also a consideration), may compromise results by limiting the number of samples examined.

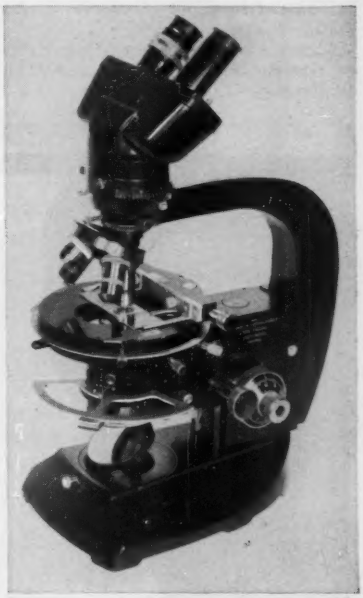
Improved conditions for recording counts can be obtained by use of the Cooke Point and Particle Counter. A special mechanical stage is designed to move the object through a series of fixed intervals, the stage being connected electrically with a counter unit of standard type. Thus, in an area analysis of a micro-section 20x30 mm. with stage intervals 0.1 mm. apart and traverses 1 mm. apart, a total of 6000 points would be semi-automatically recorded. Up to twelve points per second can be recorded, but there will be delays as the counter unit is switched to count a different constituent or grain.



The instrument may also be used manually for speedy routine counting and sizing work. It is shown here with the Cooke Universal Polarizing Microscope, set up for the area analysis of a mineralogical specimen.

Biologists polarizing microscope

Many biological objects such as nerve, muscle, many plant fibres, etc., are moderately or even strongly bi-refringent. These objects can be studied with an ordinary polarizing microscope. Some specimens, however, particularly dividing cells, show only very weak bi-refringence. In order to study these specialized equipment is necessary. Very perfect extinction must be obtained and a special elliptic compensator employed.



In the Cooke Biologists Polarizing microscope a special $\lambda/20$ mica plate compensator is built into the substage, capable of rotation by an extended arm against an arc graduated from 0–120°, with a vernier reading in tenths of a degree. Special high-extinction polars are fitted to the microscope stand. With this equipment it is possible to measure with reasonable accuracy retardations down to $\lambda/1500$ (3.3A°) and to detect them down to $\lambda/3000$ (1.7A°). The mica plate compensator can be swung out of the optical train, allowing normal examination and measurement techniques when these are desired.

Mathematical Assoc. of America, Committee on Undergraduate Program in Mathematics (R. J. Wisner, Michigan State Univ., Oakland, Rochester). 30 Dec.

Metric Assoc. (R. P. Fischelis, 502 Albee Bldg., NW, Washington, D.C.). 27–30 Dec.

National Assoc. of Biology Teachers (Miss M. Beuschlein, Chicago Teachers College, Chicago, Ill.). 27–30 Dec.

National Assoc. for Research in Science Teaching (Miss E. M. Selberg, Colorado State College, Greeley). 27–30 Dec.

National Assoc. of Science Writers (H. B. Nichols, U.S. Geological Survey, Washington, D.C.). 27 Dec.

National Geographic Soc. (R. Gray, National Geographic Soc., Washington, D.C.). 30 Dec.

National Science Teachers Assoc. (Miss M. Gardner, Natl. Science Teachers Assoc., Washington, D.C.). 27–30 Dec.

National Speleological Soc. (W. R. Halliday 1117 36 Ave., East, Seattle, Wash.). 29 Dec.

Philosophy of Science Assoc. (C. W. Churchman, Univ. of California, Berkeley). 29 Dec.

Scientific Research Soc. of America (D. B. Prentice, 51 Prospect St., New Haven, Conn.). 29 Dec.

Sigma Delta Epsilon (Miss E. B. Thurman, Natl. Institutes of Health, Bethesda, Md.). 28 Dec.

Society for General Systems Research (R. L. Meier, Univ. of Michigan, Ann Arbor). 29 Dec.

Society for Industrial and Applied Mathematics (D. L. Thomsen, Jr., I.B.M. Corp., White Plains, N.Y.). 29 Dec.

Society of Protozoologists (N. D. Levine, College of Veterinary Medicine, Univ. of Illinois, Urbana). 27–30 Dec.

Society of the Sigma Xi (T. T. Holme, 51 Prospect St., Yale Univ., New Haven, Conn.). 29 Dec.

Society of Systematic Zoology (C. F. Lytle, Tulane Univ, New Orleans, La.). 27–30 Dec.

Tau Beta Pi Assoc. (R. H. Nagel, Univ. of Tennessee, Knoxville). 29 Dec.

United Chapters of Phi Beta Kappa (C. Billman, 1811 Q St., NW, Washington 9). 29 Dec.

27–29. American Economic Assoc., New York, N.Y. (J. W. Bell, AEA, Northwestern Univ., Evanston, Ill.)

27–29. American Folklore Soc., Cincinnati, Ohio. (T. P. Coffin, 110 Bennett Hall, Univ. of Pennsylvania, Philadelphia 4, Pa.)

27–29. American Geophysical Union, 1st western natl., Los Angeles, Calif. (A. N. Sayre, U.S. Geological Survey, Washington 25)

27–29. American Physical Soc., Los Angeles, Calif. (K. K. Darrow, 538 W. 120 St., New York 27)

27–29. Western Soc. of Naturalists, Eugene, Ore. (I. A. Abbott, Hopkins Marine Station, Pacific Grove, Calif.)

27–30. Institute of Mathematical Statistics, annual, New York, N.Y. (D. C. Riley, American Statistical Assoc., 1757 K St., NW, Washington 6)

28–29. American Chemical Soc., Div. of Industrial and Engineering Chemistry, Newark, Del. (Scientific Liaison Office, Natl. Research Council, Sussex Dr., Ottawa, Canada)

28–29. Linguistic Soc. of America, annual, Chicago, Ill. (A. A. Hill, Box 7790 University Station, Austin 12, Texas)

28–29. Northwest Scientific Assoc., Spokane, Wash. (E. J. Larrison, Univ. of Idaho, Moscow)

28–30. Archaeological Inst. of America, Detroit, Mich. (L. A. Campbell, 5 Washington Square N., New York 3)

28–30. Phi Delta Kappa, Bloomington, Ind. (R. S. Merkel, Indiana Central College, Indianapolis 27)

January

2–3. California Assoc. of Chemistry Teachers, San Luis Obispo, Calif. (R. Major, 1736 N. Sierra Bonita Ave., Hollywood 46, Calif.)

8–12. International Heat Transfer Conf., Institution of Mechanical Engineers, London, England. (Secretary, IME, 1 Birdcage Walk, Westminster, London, S.W. 1, England)

8–12. Society of Automotive Engineers, annual, Detroit, Mich. (R. W. Crory, SAE, 485 Lexington Ave., New York 17, N.Y.)

8–13. Central Treaty Organization, Role of Science in Natural Resources, Lahore, Pakistan. (Office of Intern. Conferences, Dept. of State, Washington 25)

9–11. Reliability and Quality Control, 8th natl. symp., Institute of Radio Engineers and American Inst. of Electrical Engineers, Washington, D.C. (Scientific Liaison Office, Natl. Research Council, Sussex Dr., Ottawa, Ont., Canada)

9–12. Radioactive Isotopes in Clinical Medicine and Research, 2nd symp., Bad Gastein, Austria. (R. Höfer, Garnisongasse 13, Vienna IX, Austria)

9–19. Synoptic Meteorology Code Problems, World Meteorological Organization,

Toronto, Ont., Canada. (WMO, 41 Avenue Giuseppe Motta, Geneva, Switzerland)

11. Role of Hormones in Protein Synthesis, Assoc. of Vitamin Chemists, Chicago, Ill. (H. S. Perdue, Abbott Laboratories, N. Chicago)

15–17. American Pomological Soc., Toronto, Canada. (G. M. Kessler, Dept. of Horticulture, Michigan State Univ., E. Lansing)

17–19. Instrument Soc. of America, winter conf. and exhibit, St. Louis, Mo. (W. H. Kushnick, ISA, 313 Sixth Ave., Pittsburgh 22, Pa.)

18–31. Tropical Cyclones, inter-regional seminar, World Meteorological Organization, Tokyo, Japan. (WMO, 41 Avenue Giuseppe Motta, Geneva, Switzerland)

22. American Ethnological Soc., New York, N.Y. (N. F. S. Woodbury, Arizona State Museum, Univ. of Arizona, Tucson)

22–23. Symposium on Perspectives in Virology III, New York, N.Y. (M. Pollard, Univ. of Notre Dame, Notre Dame, Ind.)

22–24. Institute of the Aerospace Sciences, 30th annual, New York, N.Y. (IAS, 2 E. 64 St., New York 21)

22–26. American Mathematical Soc., annual, Cincinnati, Ohio. (AMS, 190 Hope St., Providence 6, R.I.)

23. Conference on Cardiac and Vascular Surgery, New York Heart Assoc., New York, N.Y. (R. Ober, NYHA, 10 Columbus Circle, New York 19)

23–25. American Soc. of Safety Engineers, Philadelphia, Pa. (A. C. Blackman, 5 N. Wabash Ave., Chicago 2, Ill.)

23–25. Obstetrics and Gynaecology, 2nd Asiatic congr., Calcutta, India. (S. Mitra, 4 Chowringhee Terrace, Calcutta 20)

24–26. Mathematical Assoc. of America, 45th annual, Cincinnati, Ohio. (H. M. Gehman, Univ. of Buffalo, Buffalo, N.Y.)

24–26. Thermophysical Properties, symp., American Soc. of Mechanical Engineers, Princeton, N.J. (E. F. Lype, ASME, c/o Thompson Ramo Wooldridge, 23555 Euclid Ave., Cleveland, Ohio)

24–27. American Physical Soc., annual, New York, N.Y. (K. K. Darrow, 538 W. 120 St., New York 27)

25–26. Western Spectroscopy Assoc., 9th annual, Pacific Grove, Calif. (D. G. Rea, WSA, Univ. of California Space Sciences Laboratory, Berkeley 4)

25–27. Western Soc. for Clinical Research, 15th annual, Carmel-by-the-Sea, Calif. (H. R. Warner, WSCR, Latter-day Saints Hospital, Dept. of Physiology, Salt Lake City 3, Utah)

26–29. Man and Civilization: Control of the Mind—II, San Francisco, Calif. (S. M. Farber, Univ. of California San Francisco Medical Center, San Francisco 22)

28–3. American Inst. of Electrical Engineers, New York, N.Y. (R. S. Gardner, AIEE, 33 W. 39 St., New York 18)

28–3. Pan American Assoc. of Ophthalmology, interim congr., Lima, Peru. (J. M. McLean, 525 E. 68 St., New York 21)

29–30. Carbohydrates, Cellulose, and Cellulose Industries, symp., Council of Scientific and Industrial Research, Ahmedabad, India. (Director, Ahmedabad Textile Industry Research Assoc., Ahmedabad-9)

(See issue of 1 December for comprehensive list)

New Products

The information reported here is obtained from manufacturers and from other sources considered to be reliable. Neither Science *nor the writer assumes responsibility for the accuracy of the information. All inquiries concerning items listed should be addressed to the manufacturer. Include the department number in your inquiry.*

Microbalance (Fig. 1), manufactured by Sartorius-Werke (Germany), is a self-balancing instrument with electrical indication. The beam of the balance consists of two quartz arms fused onto a quartz ring. The ring carries a wire coil wound on its inside surface, and is suspended by platinum-iridium torsion wires that also serve as current leads to the coil. The coil surrounds a cross-magnetized ceramic magnet that supports another coil through which a 480-kcy/sec current flows. When the balance is at equilibrium, the beam coil is not exposed to the high-frequency field. If the beam deviates from the equilibrium position because of a weight change, a 480-kc/sec signal is induced in the beam coil. This is used as an error signal to generate a counteracting current that is applied to the beam coil to return the coil to its equilibrium position. The counter torque is proportional to the current that produces it, so that the latter is a measure of the torque acting on the beam. At maximum sensitivity, 1 μa is equivalent to 1 μg.

The object to be weighed is placed on a small pan or suspended by wire from a hook on the stirrup. Preliminary zeroing is achieved by adjusting a counterweight that compensates for that portion of the sample weight in excess of the selected range. Final correction is made by dials controlling the torsion wire.

Stability of the balance depends on

the temperature constancy of the core magnet. The latter has a temperature coefficient of 10^{-8} per degree Centigrade, so the temperature of the beam housing must be kept constant. Other temperature effects occur in both the standard and the vacuum models. The latter permits operation under vacuum or controlled atmospheric conditions. In this model, the entire mechanism is contained inside a glass body that will hold a vacuum of 10^{-5} to 10^{-6} mm-Hg. Eight ranges are provided from 0–100 μg (smallest division 0.001 mg) to 0–20 mg (smallest division 0.2 mg). An individual balance covers seven of the eight ranges. Load capacity is 1 g. (Brinkman Instruments, Inc., Dept. Sci498, 115 Cutter Mill Rd., Great Neck, N.Y.)

Dielectric constant and dissipation factor of solids or liquids are measured by this instrument. A probe, essentially a guarded capacitor, forms one leg of a bridge; a variable capacitor forms the complementary leg. In operation, a dielectric material is placed in the field of the probe. If the bridge is not balanced, a signal appears at the input of the instrument's amplifier. The signal path is split in the amplifier so that two phase discriminators may be driven. A 90-deg lag is introduced into the dielectric-constant discriminator. By resolving the unbalance signal into two components, one in phase and one in quadrature with the reference signal, it is possible to indicate, on separate null meters, which control the operator must adjust to obtain bridge balance. The dielectric constant and dissipation factor are read directly from the controls.

A flat probe for solid samples and a corrosion-resistant probe for liquid samples are available. Dielectric-constant range is 1.0 to 12.0 with accuracy said to be ±5 percent. Dissipation-factor range is 0 to 0.15 and accuracy ±(5 percent + 0.001). (Delsen Corp., Dept. Sci500, 719 West Broadway, Glendale, Calif.)

Calorimeter controller is a thermistor-actuated system consisting of the necessary power supply, bridge circuit, amplifiers, relays, electric water heater, and valves for the automatic addition of hot and cold water to adjust and control calorimeter jacket temperatures. It can be used with old or new models of the manufacturer's adiabatic calorimeters if minor changes are made in the water connections. Temperature is said to be maintained to within ±0.01°C of the bucket temperature throughout the

test period except for momentary variations of not more than 0.1°C during periods of rapid temperature rise. A stainless-steel thermistor probe in the calorimeter jacket and another in the bucket are held adjacent to the customary mercurial thermometer to sense temperature equality.

Temperature differences are utilized through a Wheatstone-bridge circuit and a photoelectric galvanometer to actuate solenoid valves that add hot and cold water in variable amounts. Hot and cold water are added alternately in small amounts when the galvanometer beam moves on and off the photo cell. When a rapid change in temperature occurs, as in a bomb calorimeter immediately after firing, the wide swing of the light beam strikes a second photocell and actuates full flow of hot water. The equipment permits manual control at any time. The hot water reservoir is made an integral part of the controller system, and flow lines are kept as short as possible to keep lags small. (Parr Instrument Co., Dept. Sci487, 211 53 St., Moline, Ill.)

Time-lapse cinemicrography apparatus is built into and on a steel desk. It includes the following major components: camera with drive, timing unit, and observation eyepiece; light source; antivibration mount. The 16-mm camera is equipped with a 400-ft magazine. The light source combines a tungsten-filament source for viewing with a variable-intensity xenon flash lamp for exposures of less than 10^{-4} sec. The camera is driven through a quick-change gear box that provides eight rates from ¼ to 32 frames per minute. The intensity of the xenon flash can be varied over a range of about 600 without alteration of its color value. A large incubator enclosure provided with a thermostatically controlled heat source maintains materials under observation at constant temperatures from ambient to 40°C. (Sage Instruments, Inc., Dept. Sci488, 9 Bank St., White Plains, N.Y.)

Calibration-transfer standard is an ac-dc voltage and current measuring instrument containing a three-dial potentiometer, light beam galvanometer, volt box, hermetically sealed oil-filled shunt box, standard cell, ac-dc transfer element, and switching circuits. Direct-reading limit of error is said to be ±0.06 percent for ac and ±0.05 percent for dc. Application of correction factors permits increased accuracy. Voltage range is up to 1500 v, current is 15 amp, and ac frequency is 20 cy to 50 kcy/sec. Adapters permit frequency range increase to 50 Mcy/sec. (Radio Frequency Laboratories, Inc., Dept. Sci480, Powerville Rd., Boonton, N.J.)

Instrument heating units are designed to maintain exact temperatures for various electronic control devices. Performance and control characteristics depend upon the desired operational functions. Controlled temperatures up to 500°F are available with power requirements ranging from 1/5 to 3 watt/in^2 of exposed oven surface. (Spec-Heating, Inc., Dept. Sci478, 13942 Saticoy St., Van Nuys, Calif.)

Signal-actuated voice recorder is designed to record a message and at the same time maintain an automatic log of the time and date that the message originated. The recording medium is ¼-in. magnetic tape operating at a speed of ⅝ in./sec to provide continuous operation for 25½ hours without changing reels. At this speed, response within 6 db is obtained over the frequency range 300 to 2600 cy/sec. Recording begins within 10 msec after a voice signal is detected. (Litton Industries, Dept. Sci438, 6601 Romaine St., Hollywood 38, Calif.)

Low-power microscope features zoom optics to provide continuous magnification from 10 to 30×. The instrument maintains constant focus throughout power change adjustments. Field of view is 0.420 in. at 10× and 0.240 in. at 30×. A cross-line reticle is supplied, and a choice of two measuring reticles is available. Direct readings are possible at all magnifications without need for interpolation. Folding tripod legs are provided for convenient transport and storage. (Bausch & Lomb, Inc., Dept. Sci447, Rochester 2, N.Y.)

Ruby rods for optional-maser applications are available in sizes that will yield cylinders ½ in. in diameter and 8 in. long, or ⅜ in. in diameter and 12-in long. The boules are 0.04-percent chrome doped and oriented with *C*-axis perpendicular to the cylinder axis. Growing cycle is 42 hr, and annealing cycle 120 hr. (Adolph Meller Co., Dept. Sci479, P.O. Box 6001, Providence, R.I.)

JOSHUA STERN
National Bureau of Standards, Washington, D.C.

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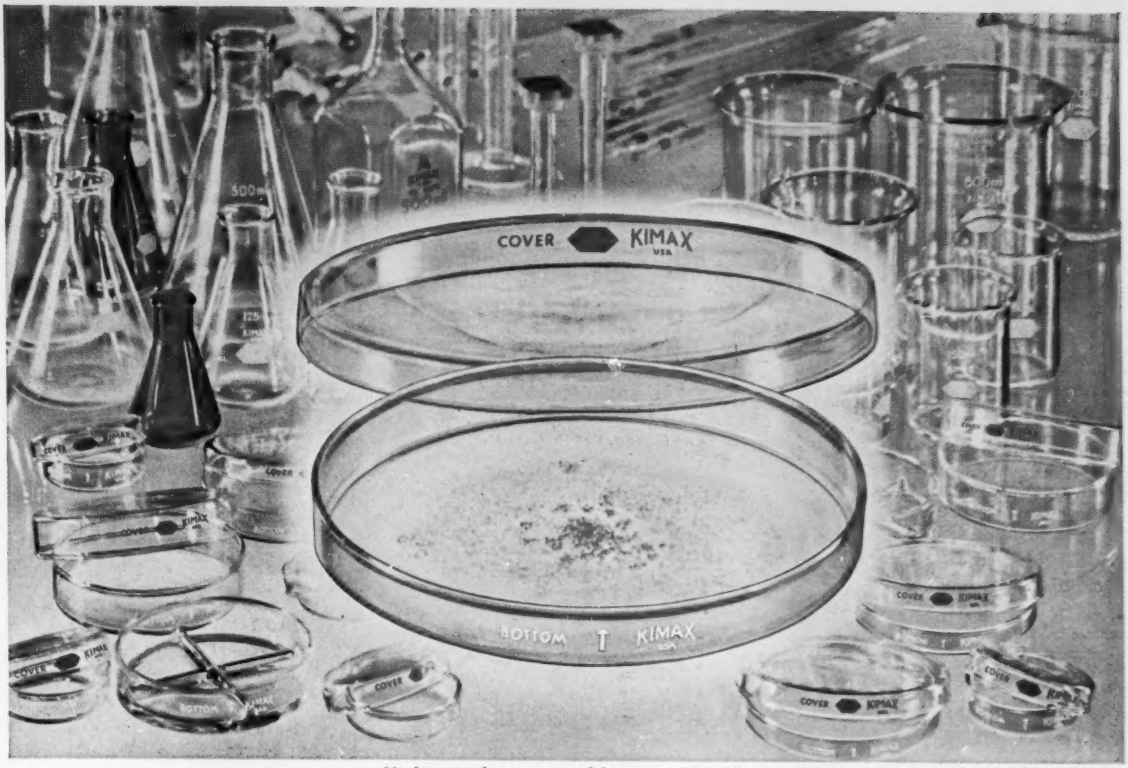

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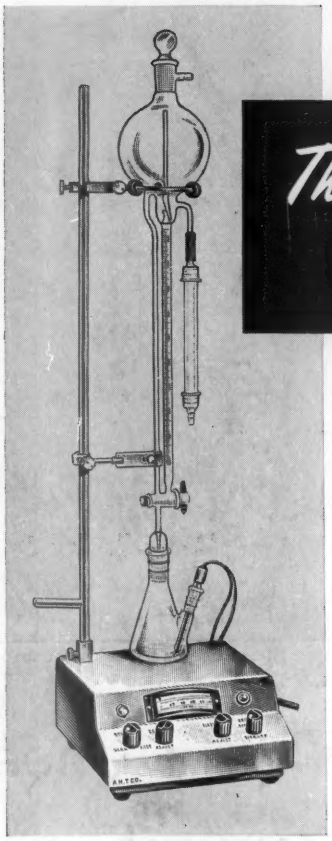

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ASTM method D-1744-60T for petroleum products

Federal Test Standard 791, method 3253 for petroleum products

Principle. In "dead stop" titration, the marked change in conductivity of the solution, when all the contained water has reacted, is detected by the electrode circuit and is indicated as a persisting, *wide deflection* of the microammeter.

Controls. Include switch, pilot lamp and rheostat for magnetic stirrer, two meter limit trimming potentiometers, and rotary switch with power off, meter zero, meter maximum, and titration positions.

Meter. Graduated 0 to 100 microamps, in 2 microamp divisions.

Electrode Unit. Two heavy gauge platinum wires, sealed into the stem of a borosilicate glass standard taper 14/35 inner joint, extend 15 mm beyond tip of stem. Lead wires connect to jacks at rear of housing.

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Overall dimensions, 12 x 12 x 40 inches high; with four rubber feet.

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